Factors Associated with Poor Outcomes when Patients with Diabetes are discharged from Hospital: A Health Informatics Approach

By

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Engineering

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Table of Contents

List of Figures and Tables

List of Figures

List of Tables

Acknowledgements & COVID-19 Impact

I would like to acknowledge the invaluable support provided by his supervisors Professor Theodoros N.Arvanitis & Dr Sarah Lim Choi Keung, who through their knowledge, efforts and support have enabled this PhD thesis to come to fruition.

I would also like to express my sincere thanks to my mentors at University Hospitals Coventry & Warwickshire NHS Trust Professor Sailesh Sankar & Professor Harpal Randeva who have provided invaluable clinical support and enabled the careful balancing of the production of this PhD Thesis alongside continued clinical work in both Diabetes & Endocrinology and General Medicine.

Finally, I would like to thank both Warwick Manufacturing Group for supporting this thesis through a WMG Studentship and University Hospitals Coventry & Warwickshire NHS Trust for not only supporting me to complete this thesis but also providing anonymised patient data to complete the thesis work.

This PhD was completed during the COVID-19 pandemic during which I returned to clinical duties to support the response at University Hospitals Coventry & Warwickshire NHS Trust in my role as a Diabetes, Endocrinology & General Medicine Registrar. The COVID-19 pandemic represented a difficult time for individuals and healthcare services internationally. It was however reassuring to see during pandemic, the potential future importance of digital health approaches, as outlined in an editorial we wrote shortly before submitting this thesis [1]. We subsequently utilised some of the informatics approaches described in this thesis to publish an article on the “COVID-19 mortality paradox” [2], attracting national press coverage [3] and forming part of a Health Data Research UK (HDR UK) submission to UK Government Scientific Advisory Group for Emergencies (SAGE) [4].

Declaration and Inclusion of Material from a Prior Thesis

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

The chapter “Systematic Review of Mortality Data” includes the results of a systematic review that was performed with Miss Teesta Mukherjee and submitted as an MSc Thesis. I acted as a second reviewer in the systematic review process, co-author on the publication and as an informal supervisor as per University of Warwick Regulations. The systematic review results are included here to enable the comparison between the systematic review of readmission risk factors (which is entirely my own work) and the systematic review of mortality risk factors. That comparison between the two reviews is also entirely my own work.

Publication & Presentation of Thesis Work

Elements of this PhD thesis have been both presented and published in peer reviewed journals or at major national and international conferences. All chapters have been written up for publication and are being submitted to peer reviewed journals, the below provides a summary of published and presented work at the time of submission.

Preliminary Work:

Presented at the Diabetes UK Professional Conference, Manchester, 2017: Secondary use of Electronic Health Records (EHRs) in diabetes research: to what extent have we unlocked their potential? [5]

Published: Robbins T, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN. Diabetes and the direct secondary use of electronic health records: Using routinely collected and stored data to drive research and understanding. Digital Health. 2018 Oct;4:2055207618804650. [6]

Chapter 1&2: Introduction & Research Approach:

Presented at the Academy of Medical Royal Colleges Annual Clinical Academics In Training Conference, Edinburgh, 2018: Demographic determinants of risk in diabetes: unlocking the potential of applied data analytics research [7].

Presented at the North European Young Diabetologists Conference, Zuiderduin, Egmond aan Zee,The Netherlands, 2018. Winner of the UK Presentation Prize: Crossing data boundaries to enable patient-specific risk stratification at the point of discharge from hospital for people with diabetes [8].

Chapter 3: Systematic Review of Readmission Risk

Published: Robbins T, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN. Risk factors for readmission of inpatients with diabetes: A systematic review. Journal of Diabetes and its Complications. 2019 Jan 30. [9]

Chapter 4: Comparing Readmission & Mortality Risk

Submitted: Mukherjee T*, Robbins T*, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN (*joint first authorship). A systematic review considering risk factors for mortality of patients discharged from hospital with a diagnosis of diabetes. Journal of Diabetes & It's Complications. 2020. *[Submitted].* [10]

Chapter 5: Standardised Effect Sizes

Presented at the Diabetes UK Professional Conference, Liverpool, 2019: A health informatics approach to risk stratification at hospital discharge for patients with diabetes: Assessing strengths of association across patient cohorts and outcomes. [11]

Accepted & In press: Robbins T, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN. Application of Standardised Effect Sizes to Hospital Discharge Outcomes for People with Diabetes. BMC Medical Informatics & Decision Making. [12]

Chapter 6: Impact of Socioeconomic factors

Presented at European Association for the Study of Diabetes (EASD) Annual Conference, Barcelona, 2019: Impact of socioeconomic status on outcomes at hospital discharge for patients with diabetes. Selected for Press Release & Press Interview at the Conference. [13]

Submitted: Robbins T, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN. Impact of Socioeconomic Geography on Outcomes at Hospital Discharge for People with Diabetes. Journal of Diabetes and It's Complications 2020. *[Submitted]* [14]

Chapter 7: Impact of Biochemistry

Selected for presentation (poster & oral) at the Diabetes UK Professional Conference, Glasgow, 2020: Association between glycosylated haemoglobin and outcomes for patients discharged from hospital with diabetes. A health informatics approach. *Conference cancelled due to COVID19 (Coronavirus), approved for publication in conference proceedings.*

Submitted: Robbins T, Lim Choi Keung SN, Sankar S, Randeva H, Arvanitis TN. Association between glycosylated haemoglobin and outcomes for patients discharged from hospital with diabetes: A health informatics approach. Digital Health 2020. *[Submitted]* [15]

These National & International Presentations are in addition to local and regional presentations of the work and elements of the work.

National & International Research and Informatics Training

During the course of this PhD period Dr Robbins participated in three Fellowship schemes, gaining international experience in Digital Healthcare and Health Informatics, whilst continuing to grow his research network. These Fellowships were a Winston Churchill Memorial Trust Fellowship, an Albert Renold Fellowship and a Health Education England Topol Digital Health Fellowship.

Winston Churchill Memorial Trust Fellowship

The Winston Churchill Memorial Trust was established in 1965, on the death of Sir Winston Churchill, as a national memorial to his achievements as a national leader. To this day, close family members remain involved, and the present Chairman is Sir Winston's grandson, Jeremy Soames. Funding was gathered by public subscription from across the country in 1965, with donations large and small being offered at banks, post offices and in the post. The resulting endowment represented a national tribute to a great leader. The Winston Churchill Memorial Trust fund Fellowships to people from "all works of life" to spend time travelling abroad with the ambition "travel to learn, return to inspire."

Dr Robbins completed his Fellowship to the United States of America, exploring US approaches to digital diabetes care. The fellowship period was from the 1st September 2017 to the 30th September 2017. He spent time at Cerner Corporation, Harvard Medical School, Beth Israel Deaconess Medical School and Banner Hospital Group. His Fellowship period shaped a number of the ideas and research approaches described in this thesis and his Fellowship report is included in Appendix 2.

Dr Robbins was awarded "follow on funding" from the Winston Churchill Memorial Trust to support the implementation of his fellowship findings. He was subsequently one of 3 nationally clinicians to be awarded funding though the Winston Churchill Memorial Trust "COVID-19 action fund" to utilise the fellowship learning in response to the COVID-19 pandemic [16].

Albert Renold Fellowship

The Albert Renold Fellowship Scheme is awarded by the European Foundation for the Study of Diabetes Mellitus, which is part of the European Association for the Study of Diabetes. Albert Renold Travel Fellowships enable scientists and clinicians to travel and stay at other institutions, in order to learn specific techniques or clinical skills required for the advancement of their diabetes research project and not available at their home institution. Dr Robbins spent time at the Kronikgune Institute in the Basque Country, Spain. The Basque Country has one of Europe's most advanced integrated care health systems. The fellowship period was from the 7th October 2019 to the 26th October 2019. Currently, the Basque Country risk stratifies the anticipated healthcare needs of its population over the forthcoming year, with a particular consideration of diabetes related needs. Dr Robbins will present the findings of his Fellowship as an oral presentation at the International Conference on Integrated Care, which was due to be held in Croatia in June 2020, but will now be held virtually in September 2020 due to the COVID-19 pandemic. Dr Robbins was also able to explore and further understand the Basque Country's approaches to reducing health inequalities, which builds directly into some of the research described within this thesis. This fellowship period was particularly useful in identifying future work that can be developed from the research described in the thesis. These proposals for future work are outlined later in the PhD thesis. The report of the Fellowship is included in the thesis as Appendix 3.

Health Education England Topol Digital Health Fellowship

Dr Robbins was selected as a fellow in the inaugural Health Education England Topol Digital Health Fellowship Scheme. Professor Eric Topol is a United States physician who is widely regarded as one of the world's most influential physicians. He has written on the Digital Based Creative Destruction of Medicine [17] & Deep Learning Artificial Intelligence [18]. The Topol Fellowship Scheme was launched in 2019, in response to Topol's landmark review of digital healthcare training in the United Kingdom. The fellowship provides direct training and leadership development support for digital health fellows, guiding them towards becoming future digital healthcare leaders.

The fellowships have three key aims;

1) To equip fellows with new skills and knowledge (e.g., how to practise person-centred design, how to use Agile as a project delivery technique, how to lead digital transformation, how to design data-driven services).
2) To inspire fellows by enabling them to hear from others, who have led digital transformations and built digital health services.
3) To connect fellows to like-minded peers, digital transformation and digital health experts and people who can mentor them.

Dr Robbins commenced the fellowship in September 2019, with the fellowship being extended to February 2020 as a consequence of the COVID-19 pandemic. The Fellowship has been particularly useful in supporting Dr Robbins to ground this thesis work in the wider context of the digital healthcare and informatics in the National Health Service (NHS). During the Fellowship period, Dr Robbins was able to present work to the Health Education England – Yale University partnership programme entitled "Using Education to Prepare the NHS and Social Care Workforce to Deliver the Digital Future" [19] as well as to the Board of NHS Digital.

Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AD	Anno Domini
AMI	Acute Myocardial Infarction
AUC	Area Under Receiver Operating Characteristic Curve
BSREC	Biomedical and Scientific Research Ethics Committee
CGM	Continuous Glucose Monitoring
CKD	Chronic Kidney Disease
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis
DSN	Diabetes Specialist Nurse
EASD	European Association for the Study of Diabetes
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMBASE	Excerpta Medica Database
GAFREC	Governance Arrangements for Research Ethics Committees
GDM	Gestational Diabetes Mellitus
Hba1c	Haemoglobin A1c (Glycosylated haemoglobin)
HDR UK	Health Data Research United Kingdom
IBM	International Business Machines
ICU	Intensive Care Unit
IDDM	Insulin Dependent Diabetes Mellitus
ITU	Intensive Care Unit
MI	Myocardial Infarction
NA	Not Applicable
NHS	National Health Service
NIDDM	Non-Insulin Dependent Diabetes Mellitus

NIHR	National Institute of Health Research
ONS	Office of National Statistics
PhD	Doctor of Philosophy
PPI	Patient & Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trial
RO	Research Objective
SAGE	Scientific Advisory Group for Emergencies
SGLT2	Sodium-glucose co-transporter-2
SPSS	Statistical Package for Social Science
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
UHCW	University Hospitals Coventry & Warwickshire NHS Trust
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
USA	United States of America
WBC	White Blood Cell
WMG	Warwick Manufacturing Group

Table 1: List of abbreviations

Abstract

Background: People with diabetes are at increased risk of adverse events, whilst admitted to hospital. Significant research has characterised this increased risk. There is also evidence that patients with diabetes are at increased risk, following hospital discharge; however, much less research has considered this area. This thesis aims to explore approaches and associations to understanding the risk of readmission and mortality, when patients are discharged from hospital with diabetes.

Methods: Initial patient public involvement grounded this research in areas that were most important to patients themselves. A systematic review of known risk factors for readmission, when patients are discharged from hospital with diabetes, was conducted. A subsequent comparison was made to risk factors identified in the literature for mortality outcomes. Extraction of retrospective data was performed for all adult patients discharged, with a diagnosis of diabetes, from a major UK tertiary referral centre over a 3-year period. The data extraction and subsequent analysis were directly informed by systematic review results. Associations between risk factors and adverse events were identified and evaluated with calculation of effect size statistics.

Results: Forty-seven studies identified statistically significant risk factors for readmission. This resulted in 72 distinct risk factors divided across 7 separate categories. Similar categories could be identified when considering mortality outcomes, however a much smaller number of studies and risk factors were identified. Analysis of extracted retrospective data identified utility of effect size measures in evaluating associations, with particularly important associations noted for socio-economic and biochemistry related factors. Clear associations are reported between socio-economic status and readmission for patients with T1DM and socioeconomic status and mortality for patients with T2DM. Hba1c values are further demonstrated statistically significantly associated with 30-day readmission and 365-day mortality

Discussion: This thesis identifies new knowledge regarding negative outcomes when patients with diabetes are discharged from hospital. This understanding is important to developing interventions to reduce such outcomes. Future work will look to understand causal links between these risk factors and outcomes, as well as developing informatics-based algorithms targeting at understanding each person's individual risk.

(336 words)

Chapter 1: Introduction

1.1 Context

An ancient Greek called Aretaeus, who lived in a country called Cappadocia bordering the Euphraytes River, is credited as the first person to describe the condition of diabetes mellitus, in approximately 120AD. His observations noted the condition as "fortunately rare"; however, he identified that "short will be the life of the man in whom the disease is fully developed" [20]. Bringing to bear the power of modern medicine, we have transformed diabetes into a chronic life-long condition, with a myriad of treatment options, quite different to Aretaeus' description. Concurrently, however, the condition can no longer be considered rare, but rapidly increasing in prevalence [21]. Our approach to scientific observation has also dramatically changed and, rather than considering one individual patient at a time, we have the privilege of using health informatics methodology to better understand the risks encountered by populations of patients with diabetes. It is on that foundation that this PhD creates new knowledge of a condition, first described over 3500 years ago, but of enormous and growing importance to society in the 21st century.

Our modern definition of diabetes mellitus is that of a "group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both" [22]. Diabetes mellitus is typically divided into three separate groupings based on aetiology; Type 1 Diabetes (T1DM), Type 2 Diabetes (T2DM) and Gestational Diabetes (GDM). This classification was proposed by the American Diabetes Association in 1997, and later adopted internationally [23].

Type 1 Diabetes Mellitus is considered an immune mediated process, caused by autoimmune destruction of beta type cells in the pancreas, which produce insulin. Typically, people with this form of diabetes present earlier in life, during infancy, adolescence and early adulthood, and rapidly progress to an absolute requirement for exogenous insulin to survive [24]. The aetiology of T2DM, in contrast, is more prominently driven by resistance of body tissue to insulin secreted by the pancreas, albeit with an element of abnormal insulin secretion, which may worsen over time [24]. T2DM typically presents more insidiously, with a period where dietary control alone or oral medications may suffice in providing adequate control [25]. Newer research is suggesting aggressive calorie restriction may provide options for diabetes remission in selected population groups [26]. The third broad category of diabetes mellitus is

gestational diabetes, which represents the development of glucose intolerance during the period of pregnancy, which typically (although not always) resolves following delivery of the foetus [27]. The presence of gestational diabetes is a very strong risk factor for the subsequent development of T2DM, in later life [28]. It is important to note that as our understanding of diabetes and, particularly the underlying genetics, improves, there is increasing blurring between the definitions of diabetes categories, and identification of specific diabetes subcategories [29]. The classification of diabetes mellitus by T1DM, T2DM & GDM is however the typical approach to management in modern clinical practice, and it is on this basis that this PhD thesis is developed [25, 30, 31].

The pathophysiology of diabetes is based around the development of micro and macro-vascular complications, as a consequence of the hyperglycaemic state [32, 33]. These complications are progressive, over time, and related to the degree of hyperglycaemia. Macrovascular complications include cardiovascular disease, stroke and peripheral vascular disease [34]. Microvascular complications include retinopathy, renal failure and neuropathy [35]. Diabetic foot disease represents a combination of peripheral vascular disease and neuropathy [36]. We know that the risk of worsening diabetes complications is affected by a range of factors, including race and social deprivation [37].

There are felt to be multiple drivers, affecting the impact of race on diabetes and its complications [38]. These can be broadly divided into biological and non-biological factors [39]. The greatest focus in the research literature has been in racial differences for T2DM. Biological factors include variations in obesity, fat distribution, glucose metabolism and genetic differences different groups. When considering obesity, large scale studies have demonstrated variations in obesity levels between different racial groups, with non-Hispanic blacks and Mexican-Americans having some of the highest levels of obesity [40]. The distribution of that fat is also important, with non-Hispanic black women having greater levels of fat stored in subcutaneous tissues compared to non-Hispanic white women who have greater visceral fat storage. This has important implications on the degree of insulin resistance in each population [41]. The causation of differences in insulin sensitivity, between racial groups, is felt to be based around variations in the ability of the body to shift metabolism towards focusing on fat oxidation or reducing levels carbohydrate metabolism, in response to either dietary input or

circulating insulin levels [42]. A significant degree of this variation will likely be attributable to genetic differences, with genetic assassination studies ongoing. A number of gene associations, varying between different races, have been identified. These include ELMO1 gene for nephropathy, ADIPQ for coronary artery disease and VEGF for retinopathy; this is certainly an area where further research is needed [43].

A major non-biological driver in racial variation in diabetes is felt to be the concept of “Acculturation” [38]. Acculturation can be defined as “the process by which immigrants adopt the attitudes, values, customs, beliefs, and behaviours of a new culture” [44]. This has been shown to contribute to poorer outcomes with respect to behaviours known to influence diabetes immigrant populations, albeit potentially mitigated by variations in socio-economic status. Further behavioural drivers known to vary between racial groups, with an impact on diabetes care, include physical activity levels and smoking rates [45]. Importantly, there is also known to be complex variations in maternal health behaviours that can influence the next generation through epigenetic changes [38, 46].

There is a close interlink between socio-economic status and racial variations in diabetes. However, socio-economic status and particularly social deprivation itself can have a significant impact on diabetes complication risks, independent of race. The impact of social deprivation is thought to be highest for retinopathy and cardiac-based complications [47]. A wide range of factors are thought to contribute to the increased risk in deprived populations. These include increased rates of smoking [48], reluctance to use insulin [48], co-morbidity burden [48] and reduced use of protective medications such as lipid lowering statins [49]. Importantly, social-deprivation has been shown to exert negative influences even from an early life stage, which is particularly important given nature of diabetes as a chronic disease with accumulation of complications risks over the life-course of the condition [50].

There are currently 4 million people of all races and socio-economic backgrounds diagnosed with diabetes in the United Kingdom, with an individual diagnosed with diabetes on average every 2 minutes [51]. The incidence of diabetes is increasing at an alarming rate. In England, there is a 5% increase in incidence, annually [52]. The cost of managing diabetes, and its complications, places significant pressures on NHS services, with an estimated 10% of the NHS Budget spent on diabetes, thus

representing an annual cost in excess of £10 billion [53]. The proportional prevalence of diabetes is particularly high amongst hospital inpatients, with 18% of NHS inpatient beds occupied by people with a diagnosis of diabetes; this can rise to in excess of 30% in some hospital settings [54]. The diagnosis of diabetes is known to be a significant risk factor for poor outcomes of patients in hospital, regardless of their underlying reason for admission [55-57]. There are varied reasons suggested for the increased risks encountered with patients with diabetes, whilst inpatients. One of the most prominent risks is that of hypoglycaemia among patients treated with insulin or other hypoglycaemic agents, such as gliclazide [58]. Patients are also at risk of the consequences of hyperglycaemia, whilst inpatients, including diabetic ketoacidosis and increased plasma viscosity, causing deep vein thrombosis [59], stroke or myocardial infarction [60].

Whilst there has been considerable research, considering the risks of diabetes related to hospital inpatients, we also know that there are increased risks at the point of discharge from hospital. Indeed, the cost of excess emergency readmissions, for patients discharged from hospital, with a co-morbid diagnosis of diabetes, is over £99 million each year [61].

The process of discharge, following an inpatient admission, represents a key step or transition point during the patient journey. The discharge process is, however, highly complex and, unlike the admissions process, entry into it is disparate with no unifying points of entry, such as triage or acute admission units. This has resulted in much less research into examining the process of discharge from hospital, despite its importance. In particular, we know that the rate of emergency readmission to hospital has increased, over the last 5 years, by 23.8% [62]. Readmission rates are known to be higher amongst medical patients, especially those with chronic diseases, such as diabetes [63]. Attempts to understand the process have been published for psychiatric discharges [64], alongside patient and staff perceptions of the discharge process [65, 66]. The complexity of both the discharge process and diabetes care has until now proved a major barrier to understanding.

Literature characterising the discharge of patients with diabetes is limited, usually focusing on the failure of discharge; readmission. These sporadic studies are based, almost exclusively, with US patients and within US healthcare systems [67]. They are

difficult to compare, because of non-uniformity of definition, including reason for readmission (index condition vs. any reason), duration of follow-up, planned versus unplanned, and preventable vs. non preventable episodes, thus preventing generalisation [67]. More common is the study of diabetes as a predictor of readmission amongst a number of other medical conditions [68, 69]. A single study, using UK Hospital Episode Statistics Service (HES) data, has been conducted to consider the impact of socioeconomic data on diabetes admission and re-admission, which, although novel in its approach, is severely limited by a small number of extracted variables and with no adjustment for individual confounders, beyond age and sex [70]. Diabetes represents a data rich pathology, which facilitates investigation beyond just “readmission rates”, with glycated haemoglobin (Hba1c) being a further outcome measure to consider, following hospital discharge [71].

In recent years, healthcare has undergone an information technology revolution through the digitization of medical records [17]. This has created large amounts of routinely collected data with enormous research potential. Effectively representing a by-product of clinical care, these data include quantitative (e.g., laboratory values), qualitative (e.g., text-based documents), and transactional data points (e.g., a record of medication delivery) [17]. Diabetes, in particular, represents a data rich pathology with extractable information on glycaemic control, renal function, cardiovascular function, foot and eye health [6]. Whilst this information represents an important opportunity to improve the quality and efficiency of care, it requires an understanding of how to process and utilise such complex information. An integrated clinical informatics approach to analytics and evidence building is needed, which until this time has been limited in application [72]. A successful integrated clinical informatics approach represents the transition of large data repositories into meaningful processes and policies that improve the efficiency and quality of care delivered [73]. Healthcare as a sector lacks the skills and experience to achieve this within a short time frame; translational research across academic departments and industrial sectors will open new research approaches and methodologies to healthcare [74].

1.2 Gap in current evidence

Therefore, there exists, overall, a significant gap in the current evidence regarding our understanding of risk factors for patients with diabetes, when they are discharged from hospital. Two of the most important risk factors, when patients with diabetes are discharged from hospital, are the increased risk of readmission [63] and the high risk of mortality [75]. This evidence gap exists despite the increased availability of routinely collected clinical data, which could provide insight into associations, risks and risk factors for this population group [6]. This gap, in the research, is important, as by developing an understanding of what contributes to these risks, we know from other conditions we can then develop both risk prediction tools to identify patients at the highest risks and design/test interventions to reduce risk [76].

1.3 Patient Public Involvement & Public Engagement

It is important to involve patients and the public in research, particularly when research uses healthcare data and relates to health outcomes. In particular, patient public involvement aims to improve the appropriateness, acceptability and relevance of research, and also ensures that the research focuses on issues that are important to patients, rather than issues that are important to the public [77]. Typical Patient Public Involvement (PPI) research does not involve large numbers of participants and is typically qualitative in nature. However, it is the quality of the interaction with those PPI representatives that defines the success of PPI [78].

This PhD research has been guided by PPI based activities. The gap in the current evidence described above is an important gap for patients themselves. The subsequent development of the research question and research area was supported by working with the Diabetes UK. Initially, the author liaised with the regional Diabetes UK Office, who suggested speaking directly to the national "Diabetes Voices" programme. This programme, hosted by Diabetes UK, comprises voices from Diabetes UK members across the United Kingdom, who respond to questionnaires and surveys used to develop diabetes based services and research. Respondents are typically both those with diabetes and also their carers. Working with the Diabetes Voices Team, we co-developed a survey to members of this group. This survey is shown below in figure 1.1. Six responses were received to the survey. Some examples of the narrative responses to the survey are included below, which clearly highlight the importance of this area of research:

"There was confusion throughout my discharge"

"Little diabetes care when being discharged and no support at home"

"I did not get a plan or any care just left to leave the hospital on my own"

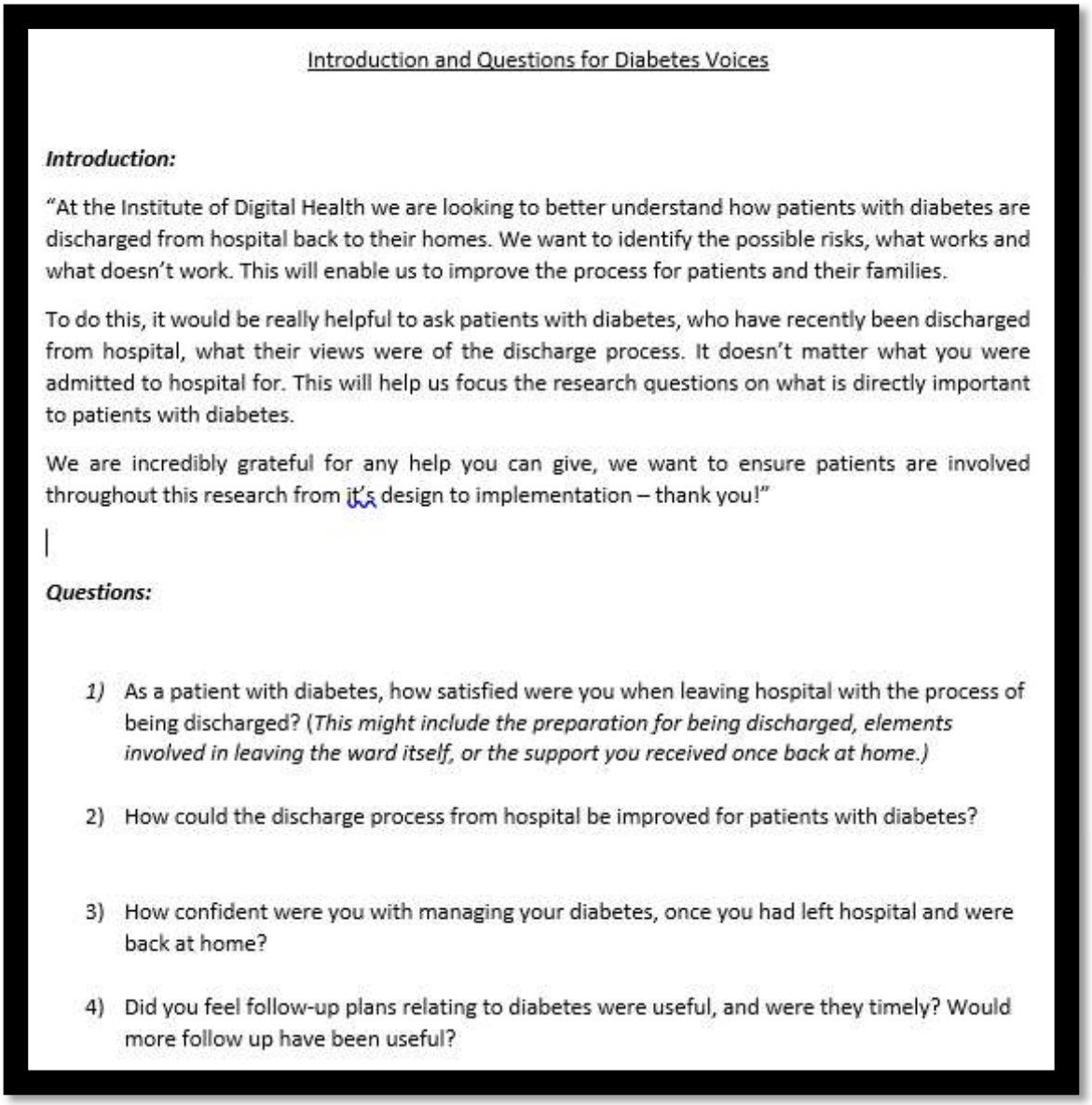
"Better follow up plans / appointments would have been useful x"

"I did not get a plan or any care just left to leave the hospital on my own"

Overall, the national survey based PPI work highlighted a number of key elements important to this work:

1) Patients see hospital discharge as a distinct process in their journey, more so than doctors.
2) Current approaches to hospital discharge are poor and do not support patients sufficiently.
3) The key to improving the discharge for patients with diabetes is providing them with the information that they need, which must be personal to them.

This preliminary patient public involvement research identified that the proposed thesis' research area is one of significant importance to patients, and that working to provide the evidence base for better information provision would be beneficial. The author of this thesis subsequently worked with the National Institute of Health Research (NIHR) Research Design Service to submit a PPI Funding Request, which was successful. This enabled the recruitment to recruit of 3 PPI members, through the "NIHR People In Research Network" to allow a more detailed critique and evaluation of this thesis' proposed research approach. Three PPI members were recruited, who each brought a different perspective to the PPI work based on their age, location and underlying diagnosis. Communication with these PPI members was both through email and telephone conversation. This helped shaped the targeting of outcome measures looking at readmission and mortality with consideration of glycosylated haemoglobin (Hba1c), being important and relevant measures for the PPI members and ones that this research has subsequently adopted.



Introduction and Questions for Diabetes Voices

Introduction:

"At the Institute of Digital Health we are looking to better understand how patients with diabetes are discharged from hospital back to their homes. We want to identify the possible risks, what works and what doesn't work. This will enable us to improve the process for patients and their families.

To do this, it would be really helpful to ask patients with diabetes, who have recently been discharged from hospital, what their views were of the discharge process. It doesn't matter what you were admitted to hospital for. This will help us focus the research questions on what is directly important to patients with diabetes.

We are incredibly grateful for any help you can give, we want to ensure patients are involved throughout this research from it's design to implementation – thank you!"

Questions:

1) As a patient with diabetes, how satisfied were you when leaving hospital with the process of being discharged? (*This might include the preparation for being discharged, elements involved in leaving the ward itself, or the support you received once back at home.)*

2) How could the discharge process from hospital be improved for patients with diabetes?

3) How confident were you with managing your diabetes, once you had left hospital and were back at home?

4) Did you feel follow-up plans relating to diabetes were useful, and were they timely? Would more follow up have been useful?

Figure 1: Diabetes UK Voices Survey Questionnaire

1.4 Overall Aim & Research Objectives

Diabetes is an important condition increasing in prevalence. In the context of a multi-morbid population, it is important we utilise existing data to better understand risks for this population of patients. This thesis builds on the identified research gaps regarding the risks, when patients are discharged from hospital with a co-morbid diagnosis of diabetes.

1.5 Research Aim

This thesis aims to explore approaches and associations to the risk of readmission and mortality, when patients are discharged from hospital with an existing diagnosis of diabetes mellitus.

1.6 Hypothesis

From the above aim, the following hypothesis is formulated: Risk factors for readmission and mortality can be identified for patients being discharged from hospital with a diagnosis of diabetes, and these can be demonstrated through interrogation and analysis of the electronic patient record.

1.7 Research Objectives

To achieve this aim and test this hypothesis, the following objectives have been identified:

1) Identify what risk factors for the readmission of patients with diabetes can be identified from the existing research literature. This is explored through the systematic review, presented in Chapter 3. [RO1]
2) Describe how the research literature differs regarding risk factors for readmission compared to risk factors for mortality, for patients being discharged

from hospital with diabetes. This is explored through the comparison between two systematic reviews, presented in Chapter 4. [RO2]

3) Demonstrate how standardised effect sizes can be used to understand factors associated with readmission for people with diabetes, including comparisons between cohorts and risk factors. This is presented in Chapter 5 and further elaborated in Chapters 6 & 7. [RO3]
4) Identify what associations exist between socioeconomic geography and poor outcomes for people being discharged from hospital with a diagnosis of diabetes? This is explored in Chapter 6. [RO4]
5) What is the association between glycaemic control and outcomes for patients being discharged from hospital with a diagnosis of diabetes? This is explored in Chapter 7. [RO5]

1.8 Thesis Structure

This PhD is structured according to the University of Warwick Doctoral College Guidelines. The introductory section establishes the context for the research and a clear aim and set of objectives, this is followed by a detailed methodology chapter. Subsequent chapters incorporate two systematic reviews and three experimental chapters, which directly meet the research objectives outlined. Each chapter cross references these research objectives and relates to the new knowledge generation summary. The experimental chapters consider the use of standardised effect size measures, the impact of socio-economic status on outcomes and finally an analysis of biochemistry values on patient outcomes. The final elements of the thesis bring together the learning through a detailed discussion section and overall conclusion.

1.9 New Knowledge Generation

This research directly creates new knowledge regarding the association between risk factors and outcomes for patients being discharged from hospital, with a diagnosis of diabetes. The new knowledge generated includes:

1) A systematic understanding of known risk factors for readmission in the currently published research literature [9].
2) A systematic understanding of differences, in the systematic research literature, between risk factors for readmission and mortality for patients being discharged from hospital with a diagnosis of diabetes [10].
3) New knowledge regarding the strengths of association between different risk factors identifiable from a typical electronic health record, for different cohorts of patients being discharged with diabetes and in relation to different outcomes [7, 11, 12].
4) New knowledge regarding the association between socioeconomic geography and negative outcomes, when patients with diabetes are discharged from hospitals with diabetes [13, 14] .
5) New knowledge regarding the association of glycaemic control and time to testing with poor outcomes when patients are discharged from hospital with a diagnosis of diabetes [15].

Chapter 2: Study Design

2.1 Rationale for Study

This PhD aims to use routinely collected electronic patient data, to form the foundation of developing new knowledge regarding the risks associated with negative outcomes when patients are discharged from hospital, with a diagnosis of diabetes. This understanding will help inform both clinicians and patients themselves, regarding risks when being discharged from hospital, whilst also supporting the development of targeted interventions. Furthermore, the new knowledge generated, during this PhD, will enable further research work that develops rigorous risk prediction models for patients being discharged from hospital with a diagnosis of diabetes. These risk prediction models will enable policy makers and clinicians to target limited resources to those patients at the highest risk of poor outcomes, when discharged with a diagnosis of diabetes. Therefore, it is essential that this research is performed prior to attempting to develop risk prediction algorithms without a firm pre-specified evidence based foundation. Indeed, algorithms for identifying patients at risk of readmission have been published [79, 80]. These describe multivariate logistic regression approaches, applied across all diseases/specialisms (not focused on one condition or group of conditions e.g., diabetes). Despite (or perhaps because of) the broad patient population included, they only considered a small fraction of factors postulated to be implicated in the discharge process [81, 82]. Consequently, these studies report only a limited predictive capacity, with area under the receiver operator curve (AUC) values of 0.65 to 0.68, with no other studies demonstrating better predictive capacity to the best knowledge of the author. The AUC is recognized as “the measure of a diagnostic test’s discriminatory power” [83], where a value of 1.00 represents a theoretically perfect test, and a value of 0.5 representing no discriminative value [83]. Developing a better understanding of pre-specified factors, associated with negative outcomes in a condition specific manner, may support the future development of more effective risk prediction models. Based on this rationale and ambition a research approach was designed by Dr Robbins, which is described in the next section.

2.2 Study Design & Research Approach

The overall study design approach is demonstrated visually in Figure 2 below. The design is grounded on the foundation of two systematic reviews presented at the start of this thesis. The systematic reviews are highlighted in blue representing their importance to the research approach. A systematic review can be defined as “A type of research synthesis that are conducted by review groups with specialized skills, who set out to identify and retrieve international evidence that is relevant to a particular question or questions and to appraise and synthesize the results of this search to inform practice, policy and in some cases, further research [84].“ High quality systematic reviews should be conducted in accordance with the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement [85]. This is a checklist and flow diagram that helps authors improve the reporting of systematic reviews and meta-analysis. A particularly important element of the PRISMA approach is the assessment of paper quality. In this thesis, the approach to quality assessment is fully described in Chapter 4 and incorporates both the quality assessment approaches described in PRISMA and the 5 C’s (category, correctness, context, contribution & clarity) approach, promoted by S.Keshav and routinely used in the engineering and computing literature reviewing [86]. Both systematic reviews are performed and described in accordance with the PRISMA statement and include rigorous quality assessment.

The first systematic review in this thesis considers risk factors for readmission, when a patient is discharged from hospital with diabetes, and forms chapter 3 of the thesis. The chapter directly answers the first research question described above: “What risk factors for the readmission of patients with diabetes can be identified from the existing research literature?”. In doing so, directly collates new knowledge from the existing research literature.

The third thesis chapter considers the second research question: “How does the research literature differ in regarding risk factors for readmission compared to risk factors for mortality for patients being discharged from hospital with diabetes?”. The chapter presents the results of a systematic review considering mortality and hospital discharge for patients with diabetes and compares this, in detail, with the results of the first systematic review, which considers readmission. For both review chapters, a

decision was made not to perform a meta-analysis. A meta-analysis can be defined as “a statistical procedure that integrates the results of several independent studies considered to be ‘combinable’ ” [87]. The studies, identified during the literature review and described in the relevant chapters, are too varied and diverse to be readily “combinable” into a meta-analysis. This is a likely consequence of the early stage nature of the research literature in this area, as explored later in this thesis.

However, the two systematic reviews are important, because the knowledge generated from these review chapters subsequently informs the data extraction process for the thesis. These extracted data form the basis of the next three experimental research chapters presented in this thesis.

The diagnosis of diabetes was taken from the coding of patients at discharge and, thus, if there was discrepancy in the diagnosis within the record, the latest diagnosis of diabetes at discharge was used. Maternity patients were excluded from the study, due to the differing nature of maternity care and readmission patterns. Patients, discharged within the last 6 months of the study period, were not evaluated as index patients, to ensure that all patients had a full period of 6 months follow up on the electronic health record, in order to assess for the outcome measures of interest.

These data are used in the fourth chapter of this thesis to answer the research question “How can standardised effect sizes be used to understand factors associated with readmission for people with diabetes, including comparisons between cohorts and risk factors” and generates new knowledge regarding the strengths of association between different risk factors identifiable from a typical electronic health record for different

The fifth chapter of the thesis represents the first assessment of the impact of socioeconomic status on the risk of readmission and mortality, at the point of discharge from hospital for people with diabetes. It, therefore, directly considers the research question “What associations exist between socioeconomic geography and poor outcomes for people being discharged from hospital with a diagnosis of diabetes?” The chapter presents exciting new findings on the differential impact of socioeconomic status on different pre-specified cohorts of patients with diabetes.

The final experimental chapter (chapter 6) represents a more exploratory piece of research, looking to better understand the research question posed around the use of

glycaemic control on outcomes, when patients with diabetes are discharged from hospital. In this chapter, the impact of glycated haemoglobin, both prior to and following discharge, in relation to outcomes of interest is considered. This chapter directly creates new knowledge, based on the use of Hba1c measures; but also leads the way for future research, when wider data are either available on new measures of glycaemic control, including continuous blood glucose monitoring and interstitial glucose monitoring.

The discussion chapter brings together these themes, highlights the strongest associations with the outcomes of interest alongside a detailed description of the strengths and limitations of this research approach. In particular, the discussion chapter extends the discussions of future work proposed in chapter 6, considering how the new knowledge generated within this research can be used as the foundation for the development of automated risk predication tools that directly support the improvement of clinical care outcomes. Included within this chapter is a discussion regarding recommendations about how the work could be used to inform: a) the healthcare service (i.e. how discharge could be improved by future follow-up work), b) health informatics (i.e. what health IT professionals can learn about better supporting similar studies in the future, and c) the clinical impact and exploitation of the results of this study (i.e. the work provides some solid early results about risk factors).

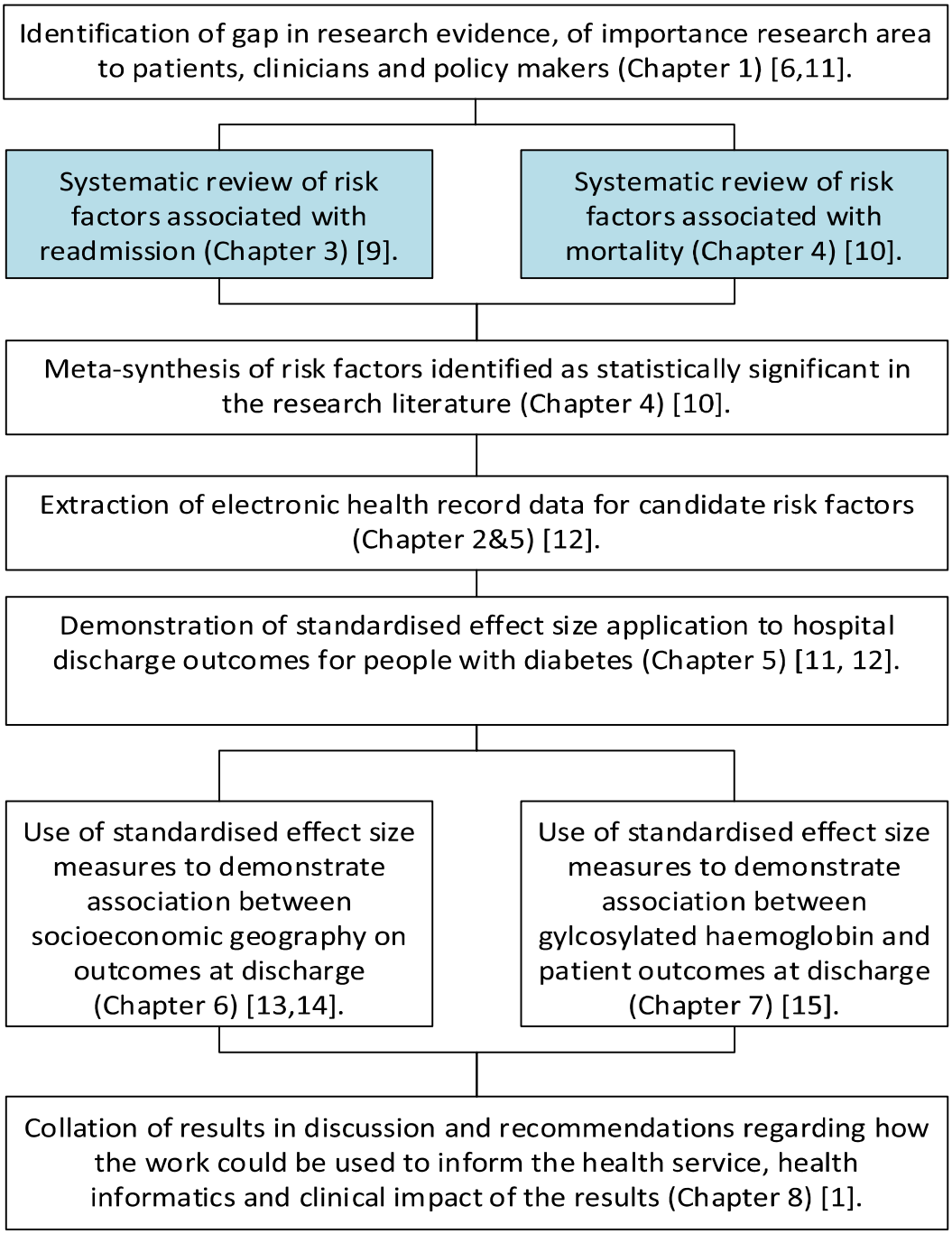


Figure 2: Summary of research design & approach

2.3 Research Data & Context

Routinely collected respective data were extracted from University Hospitals Coventry & Warwickshire NHS Trust (UHCW). Data were extracted for all adult (aged 18 or over) patients discharged from UHCW with a diagnosis of diabetes, over a 3-year period from October 2014 to October 2017. The variables extracted were informed based on the systematic literature reviews and are described in more detail in chapters 3 & 4. Outcome variable data were extracted for hospital readmission and mortality. Data were extracted by UHCW's Performance and Programme Management Office (PPMO) for the requested variables from the Clinical Results and Reporting System (CRRS) used at UHCW and anonymised before being passed to the researcher Dr Tim Robbins. The CRRS system is a bespoke "home-grown" electronic health record [88] designed and developed in house at UHCW. The PPMO enabled extraction approach follows the robust methodologies used by the Trust to extract and submit data to both the Care Quality Commission [89] and NHS England. This data extraction approach from CRRS has been used in a broad range of research studies [90-92]. Due to the ethical restrictions the author was unable to interrogate the electronic health record system directly. Patients were identified based on coding of diabetes on discharge letters, with the coding system used relating to the ICD-10 codes E10 (Insulin dependent diabetes), E11 (non-insulin dependent diabetes), E12 (malnutrition related diabetes mellitus), E13 (other unspecified diabetes mellitus), (E14 (unspecified diabetes mellitus). These codes were selected based on the broad coverage all potential codes used when patients with diabetes were discharged from hospital. The limitation associated with this approach are discussed in more detail in Chapter 8.

The data extracted included 55,826 discharges, with a mean average patient of 66.5 years (median 69, Inter-quartile range 12). There were 5117 discharges for patients with T1DM and 47786 for patients with T2DM. 53% of patients were male. The mean average length of stay was 4.16 days.

University Hospitals Coventry & Warwickshire NHS Trust is a major 1174 bed tertiary referral centre in the West Midlands region of the United Kingdom. The trust provides acute inpatient care and treatment for specialties including cardiology, cardiothoracic surgery, care of the elderly, dermatology, diabetes, ear nose and throat, gastroenterology, gynaecology, haematology, neonatal intensive care, nephrology,

neurology, oncology, ophthalmology, plastic surgery, renal medicine, respiratory medicine, rheumatology, stroke, and urology. The Trust has approximately 151,028 inpatient admissions per year, with 918,932 outpatient appointments and 236,620 accident and emergency attendances [93].

The population served by this organisation is very diverse. There are 366,800 people living in Coventry, representing the second fastest 10-year growth rate of all local authority areas, outside of London. It is felt the primary driver for this population growth is international migration. Coventry's population has a younger profile than England in general with an average age of 32.1 years compared to 39.9 years across England [94]. The latest census reported that 66.6% of Coventry's population is White British compared to a West Midlands average of 79.2% and national figure of 79.8%. The second largest ethnic group, in Coventry, is Asian British (16.3%), followed by White Other (7.2%) [95]. It is important to note when considering obesity research that this is an area with high levels of obesity, with Public Health England estimating that 64.8% of the adult population in Coventry are overweight or obese [96].

2.5 Ethical Approval

The research and methodological approach uses routinely collected anonymised patient data to build an understanding of factors associated with poor outcomes when patients are discharged from hospital with a diagnosis of diabetes. The research approach was approved by the University of Warwick's Biomedical & Scientific Research Ethics Committee (BSREC) [Study Ref: REGO-2017-2114] and University Hospital Coventry & Warwickshire NHS Trusts Governance Arrangements for Research Ethics Committees Process (GAFREC) [Study Ref: GF0220]. The ethical approvals are included in Appendix 4.

Chapter 3: Systematic review of risk factors for readmission of patients with diabetes

3.1 Introduction

People admitted to hospital have higher rates of diabetes than the general population. In the United Kingdom, 17% of inpatients have a diagnosis of diabetes mellitus [97]. Irrespective of the initial reason for admission, inpatients with diabetes act as a distinct cohort of patients with shared risk factors for adverse events [98]. People with diabetes are at a significantly increased risk of readmission, following discharge [63, 99]. Hospital readmissions rates are a psychological and physical burden to patients, and a financial burden on healthcare systems [100]. Despite the importance of readmission amongst people with diabetes, there has been limited research in this area [101]. Specifically, no published studies have attempted to identify, in a systematic way, risk factors relating to readmission for this cohort of patients.

Understanding risk factors relevant to patients, discharged from hospital with diabetes, is important to patients, carers, healthcare practitioners and researchers. It supports the delivery and development of individualised medicine, based on each patient's underlying risks; supports our understanding of regional variations in readmission risk; and supports development of evidence based interventions, targeted at reducing readmission risks [102]. Interestingly, the paucity of research in this area, for diabetes, is in direct contrast to other medical conditions, such as heart failure [103]. The systematic identification of risk factors known to be relevant to patients with diabetes is important also for this PhD thesis, as it provides a foundation for subsequent data extraction and analysis (Chapters 5 to 7), ensuring that the process is pre-specified rather than a random amalgamation of possible risk factors.

This chapter therefore aims to identify, systematically, known risk factors for readmission to hospital, among people with diabetes. The intention of the study is to cast a 'broad net', ascertaining all known risk factors, irrespective of whether identified for a specific subset of patients (such as emergency admissions only) or generalised populations of all inpatients with diabetes.

This knowledge will be essential to the planning of future diabetes services, at both an inpatient and community level [101]. This is because it will provide potential targets for improving care, reducing readmission and reducing costs. Readmissions, in particular, are very costly to the healthcare service and expose patients to the risks associated

with hospitalisation for a second time [104]. Identifying a comprehensive list of literature-derived risk factors further facilitates the development of robust pre-specified risk prediction tools. Effective risk prediction models will enable scarce resources to be targeted to patients with the greatest need. Overall, it is hoped that a better understanding of risk factors for people with diabetes will enable the development of discharge planning that is more effective, better patient education interventions, improved risk stratification tools and more targeted interventions [102].

3.2 Methods

The systematic review was conducted according to the PRISMA standards [85]. The study protocol was published in advance on the PROSPERO database (Registration Number CRD42017073773). The PROSPERO database is an international prospective register of systematic reviews aimed at reducing duplication and reporting bias. PROSPERO is funded by the UK NIHR and run by the Centre for Reviews & Dissemination at the University of York [105].

Search Strategy

A literature search was performed using EMBASE & MEDLINE databases. The search terms selected were “diabetes” AND “readmission.” The search strategy included papers published between August 2006 and August 2018; this wide date range was to ensure that the extracted studies represented current clinical care practices, given historically elongated lengths of stay and differing discharge practices. All study designs were included, with studies limited to English language articles. Due to differing obstetric and paediatric care practices, articles were restricted to adult, non-obstetric patient cohorts. Hand searching of references was performed to identify additional studies for inclusion.

Study Selection

An initial review of all studies, identified by the literature search, was completed by two authors, the leading author was the author of this thesis. Abstracts and titles were reviewed; those papers, not including information regarding risk factors for readmission to hospital in people with diabetes, were removed from the selected studies. Any discrepancies in article selection would be resolved by discussion, involving a third author to maximise the rigour of the approach. However, the work was led by this thesis’ author. All studies selected after the initial screening were reviewed as full text articles, with exclusion of those that did not identify risk factors for readmission, did not consider diabetes, or solely considered diabetes as a risk factor for another condition.

Data Extraction & Quality Assessment

Data were extracted to a pre-piloted data collection form (Appendix 5). The pro-forma collected information based on the country within which the study was conducted; whether the study was collected at a local, regional or national level; the extent of inpatient data sources, compared to community or social care data sources; the subset of patients with diabetes included in the study; risk factors that were found to be statistically significantly associated with readmission, alongside risk factors that were identified, but not tested for statistical assessment. Data were collected on the definitions of readmission used by different authors, in particular the time periods elapsed between admission and discharge, alongside an evaluation of approaches used to assess effect sizes of the risk factors identified. Data also collected on Keshav's "5 C's", an approach to reviewing journal articles used by the engineering and computing research community and therefore highly relevant to research articles considering extraction of data from clinical information systems [86]. The 5 C's include;

1) Category: What type of paper is this
2) Context: Which other papers is it related to?
3. Correctness: Do the assumptions appear to be valid?
4. Contributions: What are the paper's main contributions?
5. Clarity: Is the paper well written?

Quality assessment for each of the selected papers was performed according to the PRISMA Statement approach. This quality assessment was summarised through the 5 C's approach and included consideration of sample size, evidence to justify the sample size, appropriateness of any statistical tests applied, study recruitment and assessment, with overall narrative assessment of quality. The aim of this review is to assess the state of the literature regarding currently understood risk factors for readmission of people with diabetes, and thus no studies were excluded based on low study quality; rather a description of study quality is provided within the results section.

Data Synthesis

The diversity of definitions of readmission used in the research literature, alongside diverse subsets of people with diabetes in different studies, precludes any attempt at meta-analysis. Rather, a narrative summary of risk factors identified was extracted, with subsequent thematic grouping [106] of the risk factors as described in section 3.3, below.

3.3 Results

3.3.1 Search Results

The database search strategy identified 1562 articles, with an additional 10 articles identified through manual reference searching. Following abstract-based screening, a total of 122 articles were included for full text extraction and review. Forty articles were excluded following full text review, with 82 studies remaining for full analysis. The results of the search strategy are shown in figure 1.

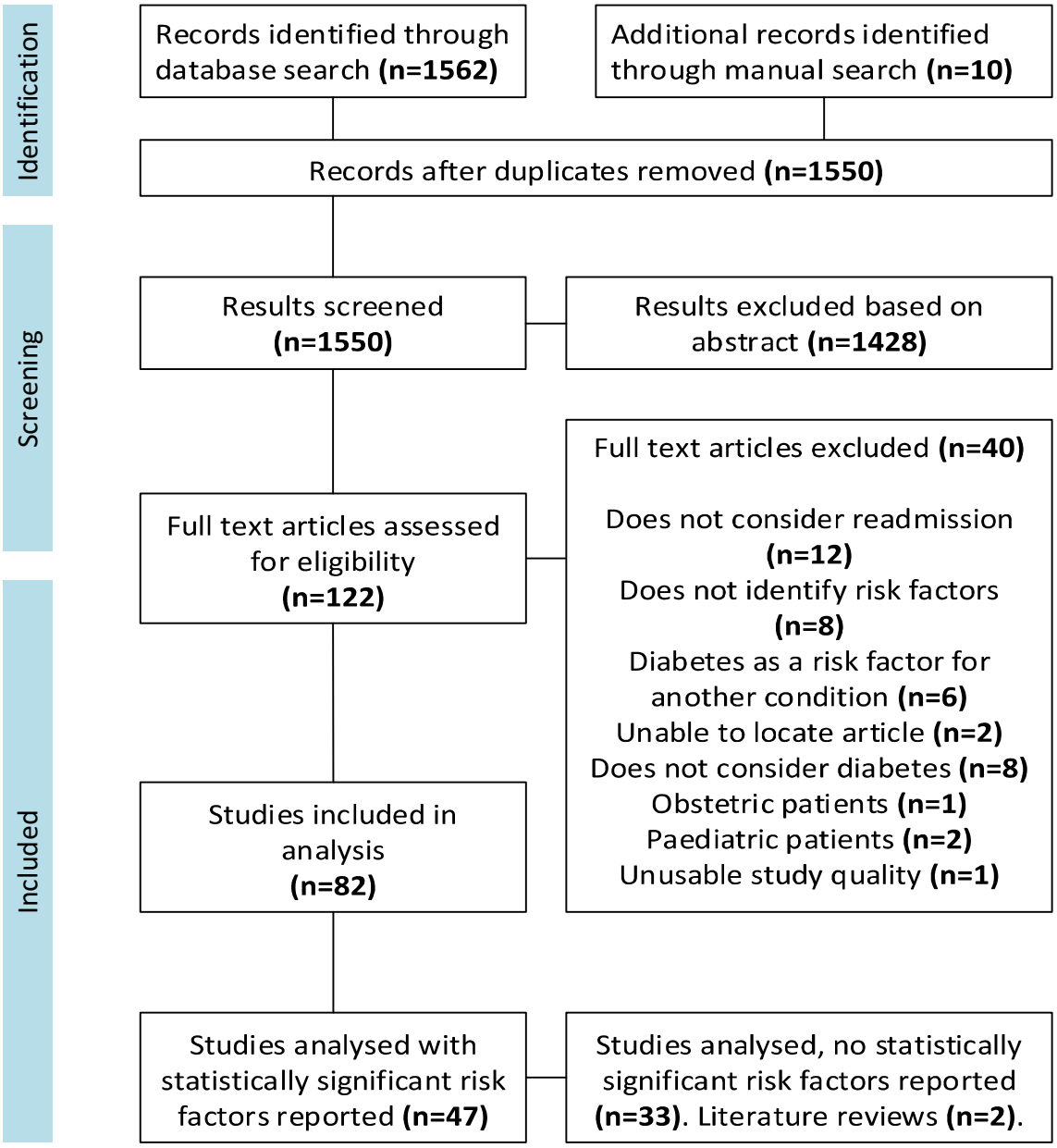


Figure 3: Flow diagram of selected studies

3.3.2 Study Characteristics

From the 82 studies identified, 69 (84%) adopted a retrospective database study design, 2 articles described non-randomised controlled studies, with a single randomised controlled trial. There were 2 prospective pilot studies, 3 prospective cohort studies, 2 case control study, one qualitative study, one systematic review and one narrative review.

The majority of studies were based on patient data from the United States of America (54 studies – 66%), with 9 studies (11%) utilising patient data from the United Kingdom. The remaining studies were conducted based on patient data from Denmark, Australia, Taiwan, Canada, China, Brazil, Italy, Israel, Japan, Saudi Arabia and Spain. One study did not clearly describe the country of origin of the patient population studied. The timing of the studies is shown in Figure 3 below, with a general increase in the number of studies published over time.

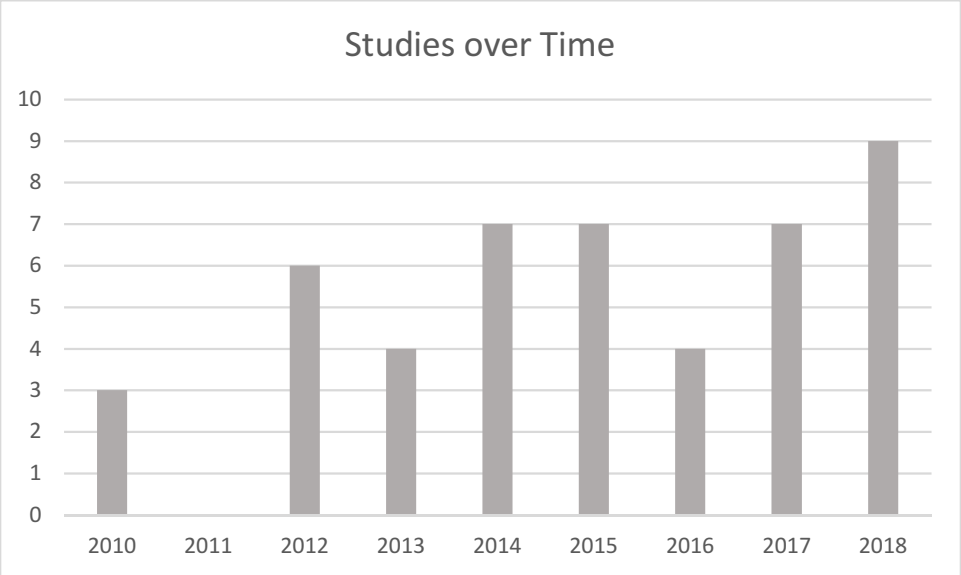


Figure 4: Number of studies published over time

Studies were predominantly conducted utilising data from a single centre (34 studies, 41%), with 18 studies (22%) utilising data from multiple centres within a single region, and 26 studies using data from a national database (32%). The study setting was unclear in two studies, and not applicable to the review articles. Studies predominantly used inpatient electronic health record sources (68 studies, 83%), with 5 studies (6%) utilising patient data from primary care or community sources and 8 studies (10%) using a combination of both community and inpatient data sources.

Forty-seven studies identified statistically significant risk factors for readmission. The characteristics of these studies are listed in Table 2 & 3; 19 studies identified risk factors in generalised populations of patients with diabetes (Table 2) and 28 studies identified risk factors for specific sub-populations of patients with diabetes (Table 3). In total, 455 statistically significant risk factors were identified across all analysed

studies, including duplicates, with a mean average of 5.62 statistically significant risk factors identified per study. When duplicates were removed, we collated 72 distinct risk factors, for readmission of people with diabetes, from the published literature. A full breakdown of risk factors, identified during the data collection process, is shown in Table 4. The risk factors are divided into whether they were identified for only a specific subpopulation of people with diabetes, or whether they were identified for generalised diabetes populations.

From the studies identifying statistically significant risk factors, there were 12 different definitions of readmission used, ranging from 7-days from index hospital discharge, to 5-years from index hospital discharge. The studies, in Table 2 and 3, are ordered by this readmission definition.

In addition to those risk factors found to have a statistically significant impact on research, 19 papers identified risk factors that had an impact on outcomes but did not reach statistical significance. This represented a total of 39 risk factors for readmission, 11 of which were unique and not identified in the list of risk factors recognised as statistically significant. These are outlined in Table 5. None of the 19 studies, identifying these non-significant risk factors, reported a power calculation to ensure they had a sufficient patient population to identify significance, if present.

3.3.3 Study Quality

Studies typically had large sample sizes of patients, with a median average sample size of 6603 patients. Seven studies, however, included less than 100 participants [107-113]. All quantitative studies described the statistical approach taken to analysing data, and these were appropriate to the study design. One quantitative study did not complete any statistical significance testing [114]. Generally, there was a failure to pre-specify which risk factors would be assessed as primary or secondary outcomes measures, and thus providing any justification for the selection of these studies. Of central importance, only 2 studies (4%) described or provided the results of a power calculation, in order to justify the sample sizes used and relevance of the subsequent statistical tests. One study was unclear regarding their description of patient recruitment and subsequent patient characteristics [115].

From the studies that identified statistically significant risk factors, 95% reported an effect size related to the risk factors identified. The effect size is “magnitude of the difference between groups” and can be reported in standardised or non-standardised forms [116]. All effect sizes in the extracted papers were reported using non-standardised statistical methods (typically Odds Ratio [117] or Hazard Ratio [118]), rather than standardised effect size measures (such as Cohen’s D [119] or Phi [120]).

There was a single qualitative study [107], which was rigorously performed with semi-structured interviews and thematic analysis. It, however, was restricted to a single (urban) centre. Twenty-three studies were conducted only in a single centre, potentially restricting their generalisability.

Ref	Author	Year	Specific diabetes sub-population?	Readmission definition (d = day, m = month, yr = year)	Sample size	Country	Study Design	No. of variables		Primary outcome
								Assessed	Significant	
[121]	X.Liu	2015	No specific subpopulation	7d to >90d	37,620	China	Retrospective cohort analysis	13	13	Readmission
[122]	S.Mokhtar	2012	No specific subpopulation	28d	1125	Saudi Arabia	Retrospective cohort & case-control	11	3	Readmission
[123]	J.Albrecht	2012	No specific subpopulation	30d	26,878	USA	Retrospective cohort analysis	7	7	Readmission
[124]	D.Rubin	2016	No specific subpopulation	30d	44,203	USA	Development & validation of risk tool	46	37	Readmission
[125]	H.Sonmez	2017	No specific subpopulation	30d	102,694	USA	Retrospective cohort analysis	2	2	Readmission and association with admission diagnosis
[126]	J.Robbins	2016	No specific subpopulation	30d	291,752	USA	Retrospective cohort analysis	31	31	Readmission
[127]	F.Zaccardi	2017	No specific subpopulation	30d	101,475	UK	Retrospective case-control study	1	1	Readmission, length of stay, mortality
[128]	J.Chen	2012	No specific subpopulation	30d	30,139	USA	Retrospective cohort analysis	39	33	Readmission
[111]	J.Swami	2018	No specific subpopulation	30d	70	USA	prospective observational study	5	2	Readmission
[129]	K.Lipska	2014	No specific subpopulation	30d	33,952,331	USA	Retrospective observational	5	2	Hyper/hypoglycaemia, hospitalization, mortality & readmission
[130]	K.Bennett	2012	No specific subpopulation	30d	94,121	USA	Retrospective cohort analysis	24	13	Readmission
[131]	J.Rubin	2018	No specific subpopulation	30d	105,791	USA	Retrospective cohort analysis	43	40	Readmission
[132]	S.Healy	2013	No specific subpopulation	30d & 180d	2265	USA	Retrospective cohort analysis	26	11	Readmission
[133]	X.Liu	2017	No specific subpopulation	30d, 60d & 90d	73,144	China	Cross sectional analysis	18	16	Readmission
[134]	L.Chwastiak	2014	No specific subpopulation	1m	82,060	USA	Retrospective cohort analysis	46	29	Readmission
[135]	H.Kim	2010	No specific subpopulation	3m	124,967	USA	Retrospective cohort analysis	32	18	Scheduled and unscheduled readmissions
[136]	J.Ena	2018	No specific subpopulation	90d	1977	Spain	Retrospective cohort analysis	21	10	Readmission
[70]	Y.Nishino	2015	No specific subpopulation	Study period	445,504	UK	Cross-sectional analysis	36	24	Admission & readmission
[115]	S.Cramer	2010	No specific subpopulation	Not declared	2633	USA	Retrospective cohort analysis	10	10	Readmission, alternative care setting

Table 2: Characteristics of studies identifying statistically significant risk factors in generalised diabetes populations (ordered by definition of readmission)

Ref	Author	Year	Specific diabetes sub-population	Readmission definition (d = day, m = month, yr = year)	Sample size	Country	Study Design	No. of variables		Primary outcome
								Assessed	Significant	
[137]	N.Wei	2013	T2DM	30d	1949	USA	Retrospective cohort analysis	1	1	Readmission & emergency department attendance
[138]	M.Engoren	2014	Diabetes and CABG	30d	880	USA	Retrospective cohort analysis	3	3	Readmission
[139]	F.Lovecchio	2014	IDDM & NIDDM post arthroplasty	30d	43299	USA	Retrospective cohort analysis	1	1	Medical / surgical complications & readmission
[112]	P.Lee	2014	T2DM & Elevated Hba1c	90d	83	USA	Retrospective cohort analysis	1	1	Readmission & emergency department visit
[140]	Z.Ries	2015	Diabetes & lower limb amputation	30d	439	USA	Retrospective cohort analysis	20	5	Readmission
[141]	Z.Li	2015	Diabetes and CABG	30d	7348	USA	Retrospective cohort analysis	1	1	Major adverse events
[142]	A.Raval	2015	T2DM aged over 65 years	30d	202,496	USA	Retrospective cohort analysis	37	20	Readmission
[143]	H.Chen	2015	Diabetes & ambulatory care	30d	120208	USA	Andersen's Behavioural Model	40	17	Readmission
[144]	D.Rubin	2017	Cardiovascular disease	30d	8,189	USA	Retrospective cohort analysis	43	36	Readmission
[145]	G.Caughey	2017	Diabetes & elderly	30d	848	USA	Retrospective cohort analysis	40	9	Readmission
[146]	J.Collins	2017	T2DM	30d	63237	USA	Development of risk prediction model	20	14	Readmission
[147]	C.Holscher	2018	Diabetic foot disease	30d	206	USA	Retrospective cohort analysis	43	6	Readmission
[148]	N.Shohat	2018	Diabetes & orthopaedic surgery	90d	3302	USA	Retrospective cohort analysis	1	1	Length of stay, readmission & mortality
[149]	D.Yu	2018	T2DM and cardiovascular disease	90d	5195	UK	Prospective study	16	15	Hospitalisation and rehospitalisation

[150]	H.Mochari-Greenberger	2014	Diabetes and cardiovascular disease	30d and 1 yr	1126	USA	Prospective study	18	1	Readmission
[151]	C.Hsieh	2015	T2DM on clopidogrel	3m, 6m & 12m	6603	Taiwan	Retrospective cohort analysis	1	1	Acute coronary syndrome and revascularisation readmission
[152]	G.Rumenapf	2013	Diabetic foot disease	1 yr	376	Germany	Retrospective cohort analysis	1	1	Readmission
[113]	L.Azevedo	2014	Diabetic ketoacidosis admitted ITU	1 yr	76	Canada	Retrospective matched cohort study	30	7	Mortality & readmission (Combined)
[153]	P.Heaton	2016	T2DM	1 yr	13,500,000	USA	Retrospective cohort analysis	17	3	Readmission
[154]	M.Kennedy	2016	Diabetes post myocardial infarction	2 yr	294	Netherlands	Multi-modal	1	1	Major adverse cardiovascular event, including readmission
[155]	E.Wu	2012	T2DM on insulin pre-admission	3 yr	2160	USA	Observational, retrospective analysis	1	1	Glycaemic control, readmission & survival
[156]	F.Hsiao	2010	T2DM & heart failure	Study period	8139	Taiwan	Retrospective cohort analysis	1	1	Death, all cause readmission, first admission heart failure
[157]	M.Isidro	2013	Diabetic ketoacidosis	Study period	152	Spain	Retrospective analysis	1	1	Multiple
[158]	E. Q. Wu	2012	T2DM, on insulin	Study period	732	USA	Retrospective cohort analysis	1	1	Clinical & cost outcomes
[159]	M.Dhamoon	2018	Stroke	Study period	25,495	Canada	Retrospective cohort analysis	2	2	Mortality, recurrent stroke, readmission
[160]	M.Arguello	2018	T2DM with sepsis	Not reported	395	Unknown	Retrospective cohort analysis	2	1	Readmission & length of stay
[161]	N.Shohat	2017	Diabetes & joint arthoplasty	Not reported	119	USA	Prospective cohort study	1	1	Surgical site infection
[162]	F.Cosmi	2018	Heart failure	Not reported	Multiple studies	Italy	Multiple studies	1	1	Mortality & heart failure rate

Table 3: Characteristics of studies identifying statistically significant risk factors for specific subpopulations of people with diabetes (ordered by definition of readmission)

Risk factors for specific diabetes subpopulations		Risk factors identified in general diabetes population	
Risk factor	Number of studies & Ref	Risk factor	Number of studies & Ref
Demographic			
Age	4 [142, 143, 146, 149]	Age	9 [121, 123, 128, 129, 131, 133-136]
Race	4 [126, 143, 144, 150]	Race	5 [70, 129, 131, 132, 134, 135]
Sex	4 [142, 146, 149, 159]	Sex	3 [115, 135, 136]
Marital status	2 [144, 153]	Marital status	1 [131]
Socioeconomic status			
Insurance type	2 [144, 146]	Insurance type	5 [121, 132-135]
Education level	1 [144]	Neighbourhood affluence	2 [70, 135]
Employment status	1 [144]	Urban home environment	2 [130, 135]
		Employment status	4 [121, 124, 131, 133]
		Education level	1 [131]
Lifestyle			
Illicit substance use	2 [126, 157]	Illicit substance use	3 [115, 128, 134]
Smoking status	2 [140, 147]		
Geographic location	1 [146]		
Patient medical factors			
Co-morbidity	5 [138, 140, 143, 146, 160]	Mental illness	6 [115, 123, 128, 131, 134, 135]
Insulin dependent diabetes	2 [139, 141]	Co-morbidity	10 [115, 121, 123, 125, 128, 131, 133-136]
Macro/microvascular disease	2 [140, 143, 144, 153]	Previous admission	5 [123, 124, 131, 134, 135]
Mental illness	2 [143, 144]	Macro/microvascular disease	2 [124, 131]
Raised Body Mass Index	2 [143, 149]	Hypogylcaemia admission	1 [127]
Hypertension	2 [147, 149]	Family history of diabetes	1 [133]
Previous DKA	1 [144]	Prior diabetes screening	1 [133]
Previous admission	2 [144, 145]	Disability index	1 [136]
Cognitive impairment	1 [142]	Cognitive impairment	1 [136]
Falls	1 [142]	Body mass index	1 [131]
		Previous DKA	1 [131]
Inpatient Stay Factors			
Active case management	1 [152]	Length of stay	7 [123, 131-135, 142]
Distance from hospital	1 [144]	Diabetes specific admission	1 [142]
Surgical procedure type	1 [154]	Diabetes education	2 [111, 132]
Penalty if re-admitted	1 [143]	Discharge destination	3 [123, 131, 135]
Support post-discharge	1 [143]	Distance from hospital	2 [124, 131]
Cardiovascular admission	1 [145]	Failure to adhere to guidelines	1 [122]
Diabetes specific admission	1 [145]	Hypoglycaemia	3 [129, 135, 136, 142]
Inpatient blood transfusion	1 [144]	Failure to record DM diagnosis	1 [126]
Enteral/parenteral nutrition	1 [144]	Hospital type	2 [121, 133]
Most extreme blood glucose	1 [144]	Previous emergency care use	2 [142, 146]
Intensive care admission	1 [144]	Cardiovascular admission	1 [142]
Glycaemic variability	1 [148]	Total cost of index hospitalisation	1 [133]
Discharge care management	1 [160]	Admitted via emergency depart	1 [134]
Medication related			
Combined PPI & clopidogrel	1 [151]	Sulfylnourea exposure	2 [131, 135]
Discharge on antibiotics	1 [140]	Insulin use prior to admission	2 [124, 131]
Medication non-compliance	1 [126]	Statin exposure	2 [128, 131]
Number of prescribers	1 [145]	Insulin during admission	2 [128, 136]

Risk factors for specific diabetes subpopulations		Risk factors identified in general diabetes population	
Risk factor	Number of studies & Ref	Risk factor	Number of studies & Ref
Thiazolidonide exposure	2 [144, 156]	Glucocorticoid exposure	2 [131, 136]
Insulin exposure	4 [144, 155, 158, 162]	Thiazolidonide exposure	1 [131]
Glucocorticoid exposure	1 [144]	Antihypertensive exposure	1 [131]
Statin exposure	1 [144]	Metformin exposure	1 [131]
Sulfylnourea exposure	2 [144, 153]		
Anti-hypertensive exposure	1 [144]		
Medication intensification	2 [112, 137]		
Speciality of outpatient physician prescribing anti-diabetic medications in community	1 [146]		
Gap in medication prescriptions	1 [142]		
Polypharmacy	1 [142]		
Laboratory Results			
Hba1c	2 [138, 149]	Hba1c	2 [131, 132]
Fructosamine level	1 [161]	Admission raised haematocrit	2 [124, 131]
Electrolyte abnormalities	1 [144]	Electrolyte abnormalities	3 [124, 128, 131, 136]
Serum cholesterol	1 [149]	Serum Cholesterol	2 [128, 131]
Admission elevated WBC	1 [144]	Admission elevated WBC	1 [131]
Serum haematocrit	1 [144]		
Serum albumin	1 [144]		

Table 4: Statistically significant risk factors identified

Additional risk factors with non-significant impact on readmission rates	Article ref
Number of primary care physicians	[143]
Living alone	[143]
Alcohol use	[163]
Failure to attend clinic appointment	[163]
Use of variable rate intravenous insulin infusion during admission	[108]
Immigration status	[164]
Elevated transaminases	[140]
Number of clinic visits	[128]
Absence of multidisciplinary team input at point of discharge	[110]
Type of beta-blocker drug	[165]
Type of community practice	[146]
Body mass index	[144]
SGLT2 exposure	[166]
Insulin type	[167]

Table 5: Additional risk factors with non-significant impact on readmission rate

3.4 Discussion

Reducing readmission risk, following hospital discharge, is a key priority for patients and policy makers across healthcare systems. People with diabetes are at an increased risk of hospital readmission. This chapter, when published, represented the first review of its kind, aiming to identify, in a systematic way, risk factors for readmission to hospital, amongst both generalised and specific populations of people with diabetes. A total of 72 distinct statistically significant risk factors were identified, with the most commonly identified being co-morbidities (15 studies), age (13 studies), race (9 studies), insurance type (7 studies), sex (7 studies). A requirement for insulin was a widely reported risk factor either before admission, during admission or subsequent to discharge.

The research literature remains at a relatively early stage of maturity, with the majority of studies representing retrospective reviews of local or regional datasets. The research is dominated by studies from the USA, which itself has a unique insurance-based approach to healthcare, and thus may not be representative of readmission patterns in other countries.

There were only two review articles that considered risk factors for readmission, one study was for a particularly specific subset of patients following cardiac surgery [168], and the other a narrative review article considering generalised diabetes readmission and preventions opportunities [101]. One study took a qualitative approach to data collection [107]. Given the nature of diabetes, as a disease of self-management, it is important that we gain a greater qualitative understanding of factors affecting readmission. The absence of qualitative studies may explain the relative paucity of psychological and patient-educational factors in the list of statistically significant risk factors extracted into Table 4.

The methodological and statistical approaches, to identifying risk factors, are also at an early stage of maturity. Whilst studies have relatively large sample sizes, there was rarely any attempt to identify the required sample sizes to meet significance testing through appropriate power calculations. This may explain the relatively low average number of statistically significant risk factors identified per study. It is a particular

concern that, this approach to statistical planning for studies may mean that a number of risk factors, which could be statistically significant, where an appropriate sample size was selected, could have been missed. The underlying variation in the patient populations described (both in the generalised patient populations and specific patient populations), alongside significant variation in the definition of readmission and use of unstandardised effect size statistical tools, precludes a meaningful quantitative meta-analysis of the effect sizes described, in order to create a “hierarchy” of risk factors, or to assess the consistency across studies identifying the same risk factors. The further comprehensive, quantitative evaluation of risk factors, will be essential to better understanding and modifying the risk factors, most relevant to patients discharged from hospital with diabetes. This thesis begins this process in chapters 5,6 & 7, directly creating new knowledge in this area.

The risk factors acknowledged in this review, demonstrate a truly diverse set of factors that significantly contribute to readmission risks in patients with diabetes. Interestingly, relatively little overlap exists between studies, with 30 risk factors (42%) being identified in just one study. Risk factors are relatively evenly distributed across the demographic, socio-economic, lifestyle, patient medical, medication related and pathology result categories described above. Forty percent of risk factors (29 risk factors) were identified in both studies examining a subset of populations with diabetes, and those identifying risk factors for generalised populations of patients with diabetes. This overlap potentially raises the argument that people with diabetes can be treated as a distinct population within the inpatient setting.

This review approach has a number of strengths including pre-registration in PROSPERO; a clearly defined, two-person search across multiple databases; assessment of study quality; semi-quantitative data synthesis; and patient and public involvement demonstrating the research question as a priority for patients. There are, however, a number of limitations that should be considered, including the fact that the review only considers English Language papers. There is also a potential limitation in the grouping of risk factors identified as statistically significant in Table 4; for example, mental health diagnoses have been grouped separately, whilst some might argue they could be considered together. The groupings have, however, been decided across the research team, and individualised references provided to support future researchers.

Concluding Remarks

This chapter identifies a number of key research priorities to better support patients at discharge from hospital with diabetes. Many of the studies reported mortality outcomes following discharge alongside readmission outcomes, and it will be important to assess the extent to which the research literature has considered mortality outcomes, given a lack of systematic review in this area. This is explored further in Chapter 4. Similarly, the inability to perform a quantitative meta-analysis of effect sizes, related to individual risk factors identified, demonstrates and important gap in the research literature.

Taken together, the literature demonstrates that risk factors can, and have in certain circumstances and often for limited groups of patients been identified for people with diabetes, being readmitted to hospital. This is a valuable resource to patients, clinicians and academics looking to improve the process of inpatient discharge from hospital. There is a clear need for statistically rigorous studies, to further understand these diverse risk factors, matched to meaningful effect sizes. This is explored further in this thesis in Chapter 5. Such research would act as the foundation for both cohorting at risk patient populations and introducing targeted personalised interventions, in order to improve the quality of care for provided for people with diabetes.

Chapter 4: Comparing Risk Factors Identified in the Published Literature for Readmission of patients Diabetes after Hospital Discharge with those Considering Mortality

4.1 Introduction

The previous chapter described a systematic review on the risk factors for readmission, when patients with diabetes are discharged from hospital. This represented the first systematic review of its kind [9]. Readmission represents only one negative outcome, when patients are discharged from hospital. Readmission is a particularly important measure, when considering hospital discharge, as it has been persistently considered as an outcome measure for the quality of hospital care, dating as far back as 1965 [169, 170], albeit with some debate [171]. Nevertheless, healthcare systems, internationally, have developed deep rooted incentive and penalty schemes for care providers, related to hospital readmission. [172-174]. Financial incentivisation has, therefore, mandated readmission rates as a priority for both policy makers and researchers.

The PPI work, upon which this PhD is grounded, is described in Chapter 2, identified that readmission rates are not the only important factor relevant to people with diabetes on discharge from hospital and indeed logically other outcome measures, such as mortality would have a very prominent importance. We know that patients in hospital are at an increased risk of mortality if they have a comorbid diagnosis of diabetes [55]. There is evidence that, where there is this increased risk of inpatient mortality, this also translates to an increased risk of mortality following hospital discharge [75, 175].

Therefore, there is a clear need to build on the first systematic review, which considers the risk factors for readmission of patients discharged from hospital with diabetes, by looking at risk factors for mortality for patients with diabetes discharged from hospital. This second systematic review's methodology was directly modelled on the methodology used in the readmission review [9], with the author of this thesis as the second reviewer to establish as systematic approach. This chapter, therefore, looks to provide a direct comparison between the two systematic reviews, in order to develop an understanding of differences between readmission and mortality outcomes, as discussed in the research literature.

This comparison is important in establishing a foundation for data extraction and analysis across the informatics elements of this thesis' research, by ensuring that the data inputted is pre-specified as equally for mortality as it is for readmission outcomes.

The research, however, has wider implications in highlighting differences between the research literature, considering readmission and, arguably, the more neglected outcome of mortality. It goes without saying that reducing mortality is of enormous interest to patients, but also to clinicians and policy makers. It is important that a diverse panel of outcome measures are given parity to enable us to develop effective healthcare processes and develop future meaningful risk stratification tools.

4.2 Methods

This systematic review was developed following the same PRISMA based methodology, as the systematic review, previously described, for readmission. This was planned to enable direct comparison between the two studies [85]. The methodology will not be repeated in this chapter, however the Search terms used to identify relevant medical literature for mortality outcomes ("mortality" or "death" or "died"). The search was performed for papers published between March 2014 to March 2019, with a subsequent update to January 2020. Data extraction was to a pre-defined and piloted data extraction form, modelled on that used for chapter 3 and included as Appendix 5. Identification of papers, data extraction and data synthesis was performed in a rigorous two-author manner. The PRISMA flowchart, shown below in figure 4, describes the search process and resulting papers identified.

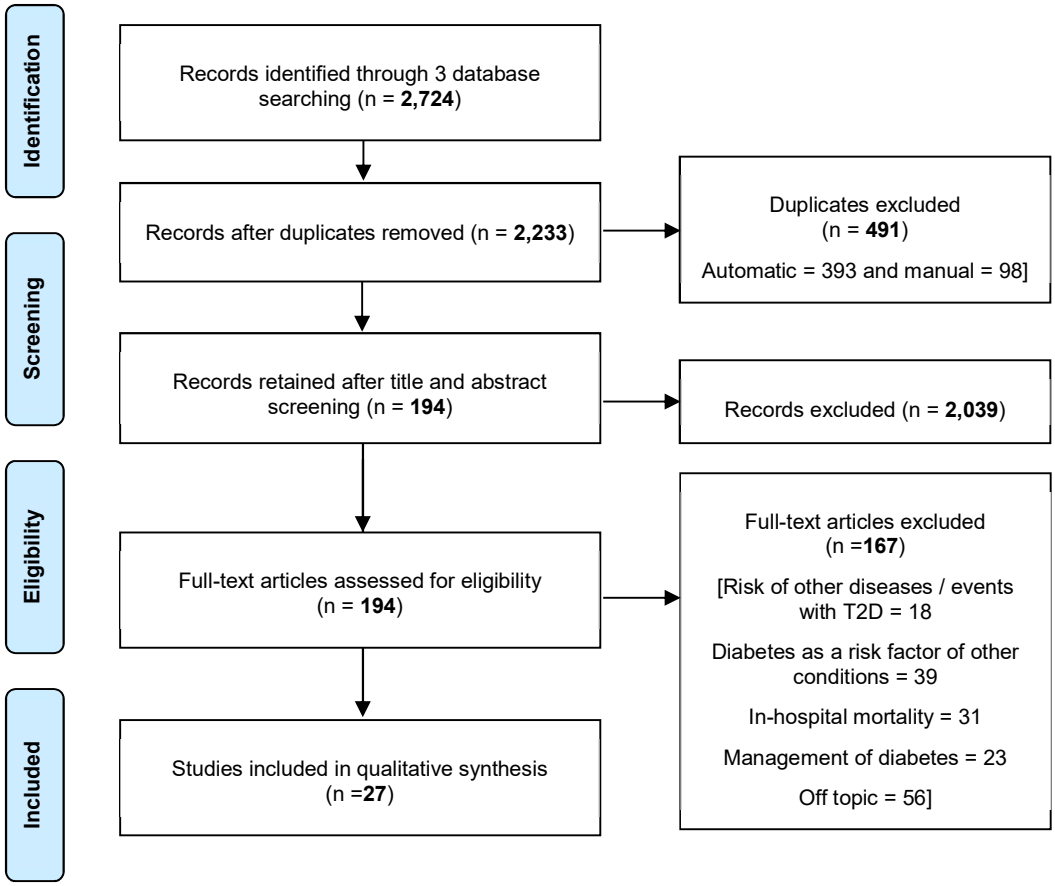


Figure 5: PRISMA Flow Diagram of Study Selection

Following identification, extraction and analysis of risks factors for mortality, the author of this thesis compared the two systematic reviews in a structured and systematic manner. This included a quantitative comparison of studies and outcomes, as well as a semi-quantitative evaluation of secondary measures, such as country or origin. Finally, to ensure a comprehensive appraisal, a qualitative comparison of study quality was performed based around the 5Cs described by Keshav (category, context, correctness, contribution and clarity) [86]. A summarized version of the results of the mortality systematic review are presented in section 4.3, followed by a detailed comparison between the two studies, which represents the main focus and output of this chapter.

4.3 Results

4.3.1 Search results

2,724 studies were identified from the literature search, representing 2,233 studies following removal of duplicates. Title and abstract based screening resulted in 2,039 articles being removed, which left 194 for full text assessment. Full text evaluation resulted in 27 articles being shortlisted for the review.

Study characteristics

From the 27 articles identified, 21 were full text articles (78%) and 6 (22%) were only in abstract form, typically from conference presentations.

The study designs noted within the review were:

Study Design	Number of Papers	Percentage of papers (%)
Retrospective study	15	55
Prospective study	7	26
Registry based	4	14
Post Hoc Analysis	1	5

Table 6: Study design

The distribution of studies over time is described in figure 2:

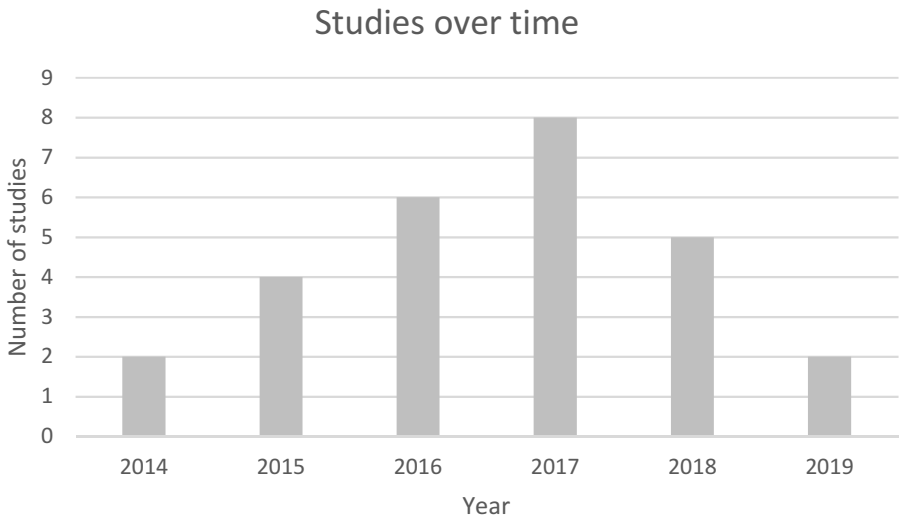


Figure 6: Publication of studies over time

3 (11%) studies were based on international datasets, 9 studies (33%) were conducted based on national data, 6 studies (23%) used regional data, 9 (33%) were single-

centre studies. The distribution of study geographies is shown in Table 7 and a breakdown of the studies is presented in Table 8.

Study Location	# studies	Study Location	# studies	Study Location	# studies
United States	3	Canada	1	Spain	1
Australia	2	China	1	Middle East	1
Brazil	2	Croatia	1	Romania & Germany	1
Greece	2	Finland	1	USA & EU	1
Italty	2	Germany	1		
Taiwan	2	Israel	1		
United Kingdom	2	Latvia	1		

4.3.2 Risk Factor Identification

The majority of studies analysed (17 studies, 63%) identified one 1 or more statistically significant risk factors for mortality, following discharge from hospital with a co-morbid diagnosis of diabetes. There were 10 studies (37%), which identified no statistically significant risk factors. The distribution of risk factors is demonstrated in more detail in table 9.

The follow up period, during which mortality was looked for in the studies, was highly variable. The most common follow up period was 12 months in 7 studies (26%). The shortest follow up period was 1 month and the longest follow up period was 9.9 years.

The extracted studies varied according to whether they considered risk in all patients with diabetes (6 studies, 23%) or a specific sub population. Those sub populations were defined either by the type of diabetes, or the characteristics relevant to the inpatient stay, and are demonstrated in more detail in table 8.

Ref	Year	Data collection	Sample size	Sub-population	Significant risk factors	No. of significant risk factors
[176]	2017	Regional	22473	Post ICU	Hospital, age, sex, ethnicity, APACHE score, co-morbidity	6
[177]	2016	National	1613	Post MI	Admission creatinine, employment, age, Hb, LVSD, Co-morbidity, activiy, in hospital revasc, BMI, insulin, fasting BM, angina freq	12
[178]	2017	Regional	59412	All diabetes	Not specific	0
[179]	2018	Single	312	Age over 60	Gait speed, calf circumference (BMI)	2
[180]	2015	Single	4607	All diabetes	Age, Gender, Cardiovascular diseases and infectious diseases (co-morbidity)	4
[181]	2014	National	1082	Heart failure	Age, co-morbidity, sodium (biochem), anaemia (haematology), medication, BMI, NHYA (severity scoring)	7
[182]	2015	National	2904	CKD and AMI admission	None	0
[183]	2015	National	4054	Admission for AMI	statins prior to AMI, number of medications	2
[184]	2018	Single	207	DKA diagnosed	Age, duration of diabetes, number of hospitalisations	3
[185]	2016	Single	409	Admitted with pneumonia	Hospitalization for pneumonia (admission diagnosis) Age, hemodialysis (procedure) Charlson comorbidity index, (score) renal insufficiency, pleural effusion, malnutrition (Co-morbidity) pH < 7.35 (biochem)	8
[186]	2017	Single	761	Admitted with poor glucose control	eGFR, Albuminuria (biochem)	2
[187]	2016	International	5005	Patients admitted with acute decompensated heart failure with diabetes	BMI (Underweight, severely obese)	2
[188]	2018	Single	304	All diabetes	0	0
[189]	2019	Regional	104525	Patients hospitalised and dispensed prescription for insulin and / or OHA within 8 days of discharge. Age >66 years	new insulin use (medication)	1
[190]	2018	Single	130	T2DM	0	0
[191]	2017	Single	304	T2DM patients with first ever noncardioemobolic acute ischemic stroke	Age, Stroke severity (NIHSS scale), Clopidogrel compared to aspirin (medication) Co-morbidity	4

Ref	Year	Data collection	Sample size	Sub-population	Significant risk factors	No. of significant risk factors
[192]	2016	National	386	DKA admitted to ITU	Age, APACHEII score (SS), mechanical ventillation, number of organs supported, DKA severity (SS), creatinine, bilirubin, pCO2 (biochem), lowest GCS	9
[193]	2016	Regional	214991	All diabetes	Age, sex, charlson index	3
[194]	2018	National	17186	Diabetes and heart failure	0	0
[195]	2016	National	1743	Diabetes and ACS	0	0
[196]	2019	National	843978	All diabetes	0	0
[197]	2017	National	71640	Diabetes and cancer	0	0
[198]	2017	Regional	28353	All diabetes	median glucose during admission & glucose variability	2
[199]	2015	International	221	T2DM admitted with ACS	0	0
[200]	2014	International	1998	Patients hospitalised with worsening heart failure and an ejection fraction below 40%	0	0
[201]	2017	Regional	218	Haematocrit, EF, ACEi. Red blood cell distribution	0	0
[202]	2017	Single	202	All diabetes	hba1c, insulin resistance	2

Table 7: Study characteristics

The statistically significant risk factors identified have been grouped, according to the same categories described within the initial readmission systematic review. This was also done alongside a grouping strategy according to whether they were identified for all patients with diabetes, or only for a specific subpopulation. In total, there were 43 distinct risk factors were identified; these are shown in table 9.

Risk Factors for Specific Diabetes Subpopulations		Risk factors in general diabetes populations	
Risk Factor	Number of studies & Ref	Risk Factor	No. & Ref
Demographic			
Age	7 [176, 177, 181, 184, 185, 188, 191, 192]	Age	2 [180, 193]
Gender	1 [176]	Gender	2 [180, 193]
Race	1 [176]		
Socioeconomic Status			
Employment status	1 [177]		
Lifestyle			
Leisure time activity	1 [177]		
Patient medical factors			
Co-morbidity	5 [176, 177, 181, 189, 191]	Co-morbidity	2 [180, 193]
Malnutrition	1 [185]		
Duration of diabetes	1 [184]		
Severity score	4 [176, 181, 191, 192]		
DKA Severity	1 [113]		
Body mass index	3 [177, 181, 187]		
Gait speed	1 [179]		
Calf circumference	1 [179]		
Angina frequency	1 [177]		
Inpatient Stay Factors			
Procedure	2 [177, 185]		
Admission diagnosis	1 [185]		
Length of stay	1 [188]		
Glasgow coma score (GCS)	1 [192]		
Mechanical ventilation	1 [192]		
Number of organs supported	1 [192]		
No. of hospitalisations	1 [184]		
Which hospital admitted to	1 [176]		
Medication Related			
Beta blocker	1 [181]		
ACEi / ARB blocker	1 [181]		
Statins prior to AMI	1 [183]		
No. of medications at discharge	1 [183]		
Insulin initiation	1 [189]		
Clopidogrel	1 [191]		
Laboratory Results			
Admission creatinine	2 [177, 192]	Hba1c	1 [202]
Fasting glucose	1 [177]		
Sodium level	1 [181]		
pH below 7.35	1 [185]		
eGFR	1 [186]		
Albuminura	1 [186]		
Bilirubin	1 [192]		
PCO2 (on blood gas)	1 [192]		
Admission haemoglobin	1 [177]		
Anaemia	1 [191]		
Glycaemic Status (not including Hba1c above)			
		Glycaemic variability	1 [198]
		Mean capillary blood glucose	1 [202]
		Insulin resistance	1 [202]

Table 8: Identified risk factors

4.3.3 Study quality

The sample size of extracted studies varied between 130 participants and 843,978 participants. The mean average number of participants, per study, was 51,445 - with a median of 1,743 participants.

All the papers used statistical tests to assess the impact of potential risk factors and evaluate their significance. Statistical significance was set at a standard of p-value less than 0.05. The majority of the papers, which was 11 in number (41%), used Cox proportional hazards model. 5 papers (18%) used univariate and multivariate Cox regression analysis, 5 papers (18%) had not defined their statistical test, 3 studies (11%) utilised univariate and multivariate analysis, 2 papers (6%) used multivariate analysis, 1 study (3%) used multivariate binary logistic regression and finally 1 more study (3%) used parametric and non-parametric tests. No studies considered the application of standardised effect size measures. There was very limited calculation of power sizes, in advance, in order to identify the appropriate population size for the studies

4.3.4 Comparison between Readmission & Mortality Studies

A summarized comparison between characteristics of readmission and mortality studies is shown in Table 10, below. The differences between these studies are elaborated further in the discussion section 4.4.

Comparator	Readmission	Mortality
Study Identification		
Total records identified	1562	2724
Studies accepted	82	27
Studies with statistically significant risk factors	47	16
Study Characteristics		
Retrospective study design	84%	55%
Qualitative studies	1	0
Number of RCTs	2	0
Qualitative Studies	1	0
Median sample size	6603	1743
Measure of duration of follow up		
Total number of countries contributing data		
Number of studies from UK data	9 (11%)	2 (7%)
Number of studies from USA data	54 (66%)	3 (11%)
Proportion of studies single centre	34 (41%)	9 (33%)
Generalised population of patients with diabetes	19 (23%)	4 (15%)
Specific population of patients with diabetes	28 (77%)	23 (85%)
Studies reporting standardised effect sizes	0	0
Risk Factors Extracted (Statistically Significant)		
Mean average risk factors per study	5.62	2.56
Total number of statistically significant risk factors	72	43
Risk Factors Identified per Category		
Demographic	4	3
Socioeconomic	5	1
Lifestyle	3	1
Patient medical	16	9
Inpatient stay	23	8
Medication	16	6
Laboratory results	7	10
Glycaemic status	0	3

Table 9: Comparison between readmission and mortality risk factors.

In addition to these quantitative differences, it is important to consider more differences in study quality between the two groups. It is already evident that there is a substantial difference is sample sizes, with much larger sample sizes being observed for readmission, as compared to mortality studies. Similarly, when assessing the clarity and contribution of each paper, it is important to note that there was a higher proportion of abstracts within the mortality papers, as compared to the readmission papers, which had less information about the methodological approaches performed. The mortality articles included fewer reports of retrospective studies, compared to the readmission

papers. This difference is important, because many of the retrospective reviews relied on the accuracy of data inputted or collected from electronic health records. This was highlighted as a limiting factor in a number of the papers. The increased use of prospective study design, within the mortality group of papers, reduces the impact of errors present within retrospectively extracted data. However, this in turn raises concerns about how generalized the results can be, based on the specific characteristic of prospectively recruited cohorts, which, in a number of papers, were quite specific to particularly small subpopulations of patients.

4.4 Discussion

Readmission and post-discharge mortality are important negative outcomes in the context of discharge from hospitals. Clinicians, managers and policy makers are undoubtedly motivated to reduce both outcomes. However, such a motivation is more typically avoiding readmission, and this is associated with financial incentivisation.

There are clear differences, within the published research literature, between the two outcome measures. Whilst the initial search identified a far greater number of articles, considering risk factors for mortality, in comparison to risk factors for readmission, once the filtering process had been completed, only 27 articles were remaining that considered risk factors for mortality, in comparison to 82 articles for readmission. The frequent use of 28 day or 30 day readmission, as the time point for including a readmission outcome supports the potential of financial incentivisation being a driver for increased readmission-based research, given these time periods are typically used in compensation algorithms. Furthermore, there was a much higher proportion of readmission based studies originating from the United States and the United Kingdom, in comparison to mortality outcomes. Both these countries were early adopters and prominent users of readmission as a financial incentivisation measure [203, 204].

It is unlikely that financial incentivisation alone was a core driver in this difference. Importantly, the follow up time for patients to readmission was much shorter than the follow up time in studies looking at mortality. This is likely to be because readmission is a more common negative outcome than mortality, and tends to happen sooner after the index admission. Researchers selecting a quality measure, against which to evaluate the discharge process, are more likely to gain a richer dataset by looking at readmission, in comparison to mortality. Furthermore, mortality data is typically considered to be relatively low fidelity with limited accuracy of death certificates or delays, in this information being entered into electronic health records [205, 206]. These factors may also explain why a higher proportion of papers considering mortality, utilised prospective data collection methods, in comparison to those studies considering readmission (45% vs 16%).

The greater use of retrospective methodologies, for the studies considering readmission, may also explain the larger samples sizes seen in the readmission studies (median sample size 6603 vs 1743), given the retrospective methodology

would facilitate easier and more cost effective evaluation of a larger cohort of patients. Similarly, the opportunity to extract large amounts of data from electronic health records, for patients with diabetes, may, perhaps, help explain the difference in the mean average number of statistically significant risk factors, identified per paper for readmission, in comparison to mortality (5.62 vs 2.56 risk factors per study).

There exist considerable differences in the risk factors, identified between the two outcome groups. Both groups had risk factors identified for all the main risk factor categories (demographic, socioeconomic, lifestyle, patient medical, inpatient stay, medication and laboratory groups). The mortality literature was the only literature to identify an association between glycaemic status, beyond Hba1c, and a negative outcome, which is important given the increasing interest on alternative measures of glycaemic control such as time in range [207]. Importantly, however, these additional factors were only identified in one paper.[208].

Possibly, one of the most interesting differences between the two outcome groups is that, a larger proportion of the readmission papers (23% vs 15%) considered risk factors for populations of patients with diabetes, in general, as compared to specific subpopulations of patients with diabetes. This is important in planning further health informatics work, given this precedent to cohort groupings of patients with diabetes. There is, however, an important opportunity here, given that all the papers considering a subpopulation of patients with diabetes, across both mortality and readmission, consider either only one subpopulation or a close-knit grouping of subpopulations. What is was not done was to cohort a population of patients with diabetes and then analyse each cohort separately, in order to allow comparisons between the different groups. This is an opportunity that is exploited later in this PhD Thesis in chapters 5, 6 & 7.

Another important element, which supports the approach adopted in this thesis, is that across the two reviews of mortality risk factors and readmission factors, there is no overlap in the papers extracted, suggesting that no study has previously compared both readmission and mortality outcomes.

Together, the two systematic reviews, presented and compared here, provide an important foundation for this thesis. They highlight both readmission and mortality as important outcome measures, following hospital discharge, with a combined total of

over 100 papers considering risk factors relevant to these outcomes. A particularly valuable output is that the categorisation and risk factors, themselves, enable a degree of pre-specification of candidate risk factors for health informatics evaluation.

There are important limitations to the comparison of the systematic reviews presented here. The most important limitation is that there was a slight variation in the personnel conducting the reviews. The first readmission review was conducted by the thesis' author, with Professor Arvanitis as the second reviewer. In contrast the mortality review was conducted by an MSc student with the thesis' author as second reviewer. The author of this thesis then performed the comparison presented here. It could be argued, therefore, that the variation in project team could account for some of the differences seen between the studies. The author of this thesis would, however, suggest that the protocol and approach developed, in the readmission review, has been closely followed here, supervised by the author himself, so any structural variation is likely to be minimal. The second important limitation is in the process of the literature search itself. The search was limited to English Language papers, over the last 5 years and only articles published in the published research literature. It is possible that there is content relating to mortality or readmission available in other sources, for example the grey literature, and that this information may not be balanced (for example, more information may be available for one outcome vs. another). It would be difficult to identify particular grey literature sources for this rea, for whilst there is an annual National Diabetes Inpatient Audit, this does not specifically look at readmission, nor have there been any National Confidential Inquiries into post-discharge mortality for diabetes. We, therefore, believe that the majority of information can be captured from the published research literature.

Concluding Remarks

Readmission and mortality are both important outcomes, following discharge from hospital with diabetes. There are clear differences in the maturity of the published literature in relation to these two outcomes. Common to both, however, is that there is a sufficient depth of literature to pre-specify candidate risk factors for subsequent data extraction and statistical analysis. The following chapters of this thesis utilise the information identified in the systematic reviews to further interrogate risk factors

for both readmission and mortality, when patients with diabetes are discharged from hospital.

Chapter 5: Application of Standardised Effect Sizes to Hospital Discharge Outcomes for People with Diabetes

5.1 Introduction

Increasing numbers of hospital inpatients have a co-existent diagnosis of diabetes [209]. These patients are at an increased risk of both readmission [210] and mortality [211, 212]. Chapters 3 and 4 have identified that multiple studies have been performed, aiming to identify statistically significant risk factors for these poor outcomes, when patients with diabetes are discharged from hospital [63, 99]. These studies typically identify risk factors for generalised populations of inpatients with diabetes [125, 126], or for specific cohorts of patients, who may have been admitted for a particular condition or group of conditions [139, 144, 147]. Almost universally, these studies report statistically significant risk factors for an individual outcomes (either readmission or mortality) and report unstandardised effect size measures, usually as odds ratios [117].

The use of unstandardised effect size measures, which report only on individual outcomes for individual patient cohorts, makes effect size comparisons between groups difficult. Comparisons between studies are additionally difficult as, unlike clinical trials, extracted electronic health record data is rarely made available as supplementary material to research articles, due to the risk of inadvertently compromising anonymity of the data. Furthermore, whilst standardised effect sizes can be calculated if both the sample size and standard deviation are given with unstandardised effect statistics in articles, it is recognised that this information is too often incomplete and can be a laborious process across multiple studies even if it is available [213].

This represents a key challenge in identifying optimal targets and outcome measures for the delivery of interventions to improve the discharge process from hospital for patients with diabetes. In particular, attempts to create risk stratification tools for patients with diabetes, at discharge, have only had limited success, often reporting only moderate area under the curve (AUC) values and restricted predictive values [124, 149].

Standardised effect size calculations allow the direct comparison between risk factors, outcomes and cohorts. Similar to other statistical tests, there are a range of effect size statistics available, with well over 60 reported in the literature [214]. The appropriate

standardised effect size statistic needs to be selected as relevant to the variables in question, with *d* statistics (such as Cohen's *d or*) appropriate for continuous dependant variables & categorical predictors, whilst differing tests are relevant for effect size estimates related to categorical data (such as Phi or Cramér's V) [215].

Effect sizes are descriptive statistics that support both clinicians and researchers to interpret study findings. The interpretation of effect sizes can be done in isolation, against pre-defined published levels of effect or "rules of thumb" [119]. Table 11 demonstrates published rules of thumb for Cohen's d [216] and Phi statistics [120, 217]. However, the importance of any effect is dependent on what is being studied, with for instance very small effect sizes being important in certain circumstances (for example life threating situations) [218]. Effect sizes statistics are also particularly valuable when looking to make comparisons, for example between different predictors, cohorts or variables. It is primarily in this context that standardised effect sizes have utility in considering risk predictors for negative clinical outcomes.

In this study, we extract data from a large tertiary referral centre in order to calculate standardised effect sizes for pre-specified risk factors, across outcome measures and across patient cohorts. This research demonstrates the importance of calculating standardised effect sizes, a practice more typical in the psychological literature than medical literature. It further demonstrates important variation in risk at discharge from hospital for patients with diabetes.

Cohen's *d*		Phi Coefficent	
Effect Size	***d* value**	**Effect Size**	***d* value**
Very small	0.01	Negligible	0.00 to <0.10
Small	0.2	Weak	0.10 to <0.20
Medium	0.5	Moderate	0.20 to <0.40
Large	0.8	Relatively strong	0.40 to < 0.60
Very large	1.2	Strong	0.60 to <0.80
Huge	2	Very strong	0.80 to <1.00

Table 10 "Rules of thumb for interpreting effect sizes"

5.2 Methods

Selected Risk Factors
Age
Sex
Co-morbidity burden
Previous DKA
Dementia
DSN review
T1DM
T2DM patients
Unknown diabetes type
Weekend Discharged

Table 11: Readily extractable pre-specified risk factors

The study adopted a retrospective evaluation of data extracted from electronic health record (EHR) of a large tertiary referral centre, in the West Midlands region of the United Kingdom, for all patients discharged from University Hospitals Coventry and Warwickshire NHS Trust with a diagnosis of diabetes, over a 3-year period from October 2014 to October 2017. Data were extracted for an exemplar set of 10 pre-specified risk factor variables. These variables were selected based on both pre-specification from the published research literature, and the ease of which data for these variables can be extracted from inpatient electronic health records. Ease of extraction was considered to ensure the results are generalizable to other healthcare organisations internationally. The selected extracted variables are listed in Table 12. Outcome variable data were extracted for hospital readmission within 30 days and mortality within 180 days of hospital discharge.

The diagnosis of diabetes was taken from the coding of patients at discharge and, thus, if there was discrepancy in the diagnosis within the record, the latest diagnosis of diabetes at discharge was used. Maternity patients were excluded from the study, due to the differing nature of maternity care and readmission patterns. Patients discharged within the last 6 months of the study period were not evaluated as index patients, to ensure that all patients had a full period of 6 months follow up on the electronic health record, in order to assess for the outcome measures of interest.

The association between risk factor variables and outcomes of interest was analysed using Chi Squared Test for categorical variables and Student's T Test for continuous variables, following adequate assessment for skew and kurtosis to ensure normality. An absolute skew value larger than 2 or an absolute kurtosis (proper) larger than 7 may be used as reference values for determining substantial non-normality [219].

A p-value of <0.05 was considered significant. Standardised size was evaluated using Phi coefficient for categorical variables and Cohen's D for continuous variables. The statistical significance and effect size were evaluated for the following patient cohorts:

all patients discharged with a diagnosis of diabetes; all emergency admissions discharged with a diagnosis of diabetes; all emergency admissions discharged with a diagnosis of T2DM; all emergency admissions discharged with a diagnosis of T1DM; all elective admissions discharged with a diagnosis of diabetes; all elective admissions discharged with a diagnosis of type 2 diabetes; all elective admissions discharged with a diagnosis of T2DM; all patients with diabetes discharged from surgical care; all patients with T1DM discharged from surgical care; and all patients discharged with T2DM from surgical care.

All statistical testing was performed using Microsoft Excel 2016 [220] and IBM's SPSS v24 [221].

5.3 Results

Data was extracted for 46,367 distinct patient episodes resulting in discharge from hospital, over the study period, with a diagnosis of diabetes. Table 13 demonstrates the number of patients in each cohort. Table 14 illustrates the statistical significance of each risk factor in relation to readmission per patient cohort, separated into categorical risk factor variables (evaluated with the Chi Squared Test) and continuous variables (evaluated using student's T Test) for readmission. Table 15, similarly, demonstrates statistical significance testing for mortality. Table 16 illustrates the standardised effect sizes of each risk factor related to readmission per patient cohort, separated again into categorical risk factors (evaluated using Phi coefficient) and continuous risk factors (evaluated using Cohen's D). Table 17 illustrates effect sizes in relation to mortality at 180 days.

Patient Cohort	Number of patients in sample
All patients discharged with a diagnosis of diabetes	46367
All emergency admissions discharged with a diagnosis of diabetes	20140
All elective admissions discharged with a diagnosis of diabetes	23379
All emergency admissions discharged from surgical care with diabetes	3032
All medical admissions discharged from surgical care with diabetes	14250
All surgical care discharges with type 1 diabetes	399
All surgical care discharges with type 2 diabetes	2547
All medical care discharges with type 1 diabetes	1455
All medical care discharges with type 2 diabetes	12498

Table 12 Patient cohorts and sample size

Statistically significant associations, with readmission at 30 days, were found for 46 cohort/risk factors combinations, with 61 statistically significantly associations for mortality at 180 days. Following expectations, the effect size of most risk factors individually on outcomes was small. However, there was significant variation in effect size between risk factors, cohorts and outcome measures. The mean average effect size for categorical values considering readmission (Phi Coefficient) was 0.05, with the mean average effect size for continuous variables being (Cohen's D) 0.22. Mean average effect size for categorical values, considering mortality, was 0.06 (Phi

coefficient) and for continuous variables 0.83 (Cohen's D). Effect sizes were notably larger for surgical cohorts of patients, in particular surgical patients with T1DM.

Assessment of statistically significant association between risk factors and readmission at 30 days.	Statistical Test	All diabetes discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	TTEST	<0.01	0.33	<0.01	0.09	0.08	<0.01	0.6	0.07	0.94
Sex	CHISQ	0.01	0.04	0.62	0.06	0.39	<0.01	0.42	<0.01	0.16
Co-morbidity burden	TTEST	<0.01	<0.01	<0.01	0.56	<0.01	<0.01	<0.01	0.07	<0.01
Previous DKA	CHISQ	<0.01	<0.01	<0.01	<0.01	0.68	<0.01	0.57	0.19	0.75
Dementia	CHISQ	<0.01	<0.01	0.05	0.09	<0.01	0.27	0.12	0.34	0.02
DSN review	CHISQ	<0.01	<0.01	<0.01	0.18	<0.01	0.05	0.38	<0.01	<0.01
T1DM	CHISQ	<0.01	<0.01	<0.01	<0.01	0.03	NA	NA	NA	NA
T2DM patients	CHISQ	<0.01	0.10	<0.01	0.06	0.46				
Unknown diabetes type	CHISQ	<0.01	<0.01	<0.01	0.15	<0.01				
Weekend Discharged	CHISQ	<0.01	0.06	<0.01	0.01	<0.01	0.44	0.03	0.29	0.36

Table 13: Assessment of statistically significant association between risk factors and readmission at 30 days. [Shaded cells reflect lack of statistical significant value of p<0.05.]

Assessment of statistically significant association between risk factors and mortality at 180 days.	Statistical Test	All discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	TTEST	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Sex	CHISQ	<0.01	<0.01	<0.01	<0.01	<0.01	0.92	0.60	0.07	<0.01
Co-morbidity burden	TTEST	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Previous DKA	CHISQ	<0.01	<0.01	<0.01	0.20	<0.01	0.01	0.65	<0.01	<0.01
Dementia	CHISQ	<0.01	<0.01	0.40	<0.01	<0.01	<0.01	0.01	<0.01	<0.01
DSN review	CHISQ	<0.01	0.02	<0.01	<0.01	<0.01	0.80	0.05	<0.01	0.31
T1DM	CHISQ	<0.01	0.09	0.14	0.34	<0.01	NA	NA	NA	NA
T2DM patients	CHISQ	<0.01	<0.01	0.01	<0.01	<0.01				
Unknown diabetes type	CHISQ	0.7	0.43	<0.01	0.09	0.82				
Weekend Discharged	CHISQ	<0.01	<0.01	<0.01	<0.01	<0.01	0.58	0.34	0.12	<0.01

Table 14: Assessment of statistically significant association between risk factors and mortality at 180 days. . [Shaded cells reflect lack of statistical significant value of p<0.05.]

Assessment of standardised effect size between risk factors and readmission at 30 days.	Statistical Test	All diabetes discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	Cohens D	0.08		0.16			0.45			
Sex	Phi	-0.01	-0.01				-0.10		0.07	
Co-morbidity burden	Cohens D	-0.18	-0.11	-0.37		-0.12	0.39	-0.17		-0.18
Previous DKA	Phi	-0.10	-0.03	-0.10	-0.08		-0.17			
Dementia	Phi	0.03	0.03	0.01		0.03				0.06
DSN review	Phi	-0.03	0.04	0.02		0.07			-0.11	0.12
T1DM	Phi	-0.06	-0.03	-0.05	-0.06	-0.02	NA	NA	NA	NA
T2DM patients	Phi	0.02		0.03						
Unknown diabetes type	Phi	0.03	0.03	0.03		0.03				
Weekend Discharged	Phi	-0.01		0.03	0.05	-0.03		0.04		

Table 15: Assessment of standardised effect sizes for statistically significant risk factors for readmission at 30 days. [Shaded cells did not reach statistical significant in Table 14]

Assessment of standardised effect size between risk factors and mortality at 180 days	Statistical Test	All diabetes discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	Cohens D	-0.76	-0.72	-0.45	-0.89	-0.70	-1.40	-0.79	-1.69	-0.56
Sex	Phi	-0.03	-0.03	-0.03	-0.03	-0.03				-0.03
Co-morbidity burden	Cohens D	-0.72	-0.64	-0.53	-0.90	-0.60	-0.86	-0.87	-1.41	-0.48
Previous DKA	Phi	0.05	0.08	0.03		0.09	0.13	0.01	0.23	0.03
Dementia	Phi	-0.06	-0.05		-0.04	-0.05	-0.16	-0.05	-0.09	-0.04
DSN review	Phi	-0.04	0.02	-0.02	-0.04	0.05			0.16	
T1DM	Phi	0.04	0.09			0.09	NA	NA	NA	NA
T2DM patients	Phi	-0.07	-0.08	-0.02	-0.10	-0.08				
Unknown diabetes type	Phi			0.02						
Weekend Discharged	Phi	-0.02	<0.01	0.02	-0.03	-0.04				-0.04

Table 16: Assessment of standardised effect size for statistically significant risk factors for mortality at 180 days [Shaded cells did not reach statistical significance in Table 15]

5.4 Discussion

In this chapter, the author demonstrated that there is substantial variation in the effect sizes, regarding risk factors related to poor outcomes at discharge from hospital for patients with diabetes. Whilst a large number of candidate risk factors have been identified as statistically significant, there is variation in the effect sizes between individual risk factors. Typically, effect sizes for mortality were greater than effect sizes for readmission, suggesting that using the risk factors described here, it may be easier to predict risk related to mortality than readmission. This is particularly interesting, given that readmission is most commonly used as the marker of the success of the discharge process and a typical target for risk predication modelling and risk reduction interventions.

There is also substantial variation in both the statistical significance and effect size of individual risk factors between cohorts of patients with diabetes, as well as the overall combined effect sizes between individual patient cohorts. This suggests, again, that risk prediction may be easier for some cohorts of patients, particularly those with T1DM & those attending for surgery. The ability, with which we are able to predict risk from known risk factors, is important in the development and appropriateness of developing risk prediction tools, but also in targeting interventions to those most at need. The targeting of interventions, supported by evidence-based discussions of risk with patients, is essential to individualised sustainable healthcare.

This part of this thesis' research does not aim to provide a comprehensive assessment of effect sizes for every patient cohort with diabetes at discharge from hospital, or for every known risk factor for poor outcomes. Rather, we demonstrate the substantial variations of standardised effect sizes between risk factors, outcomes and patient cohorts. This, therefore, lays important foundations for future research looking to explore individual risk factors, outcomes or cohorts in more depth, before possible future development of rigorous risk prediction models.

The study has a number of limitations. Firstly, it is based only at a single centre, albeit with a large patient population over a significant period of time. Secondly, we have not attempted to control individual risk factors at this stage; this approach is, however,

representative of the many studies identifying new risk factors and subsequently reporting with unstandardised effect sizes.

When considering the utility of standardised effect sizes it is notable that we have used two different effect size statistics (Cohen's d & Phi coefficient), whilst the primary aim of using standardised effect size statistics is to enable comparison the outputs of the two statistical methods cannot be directly compared due to variations in the "rules of thumb" for their interpretation. Whilst some processes to enable conversion between effect size statistics have been published, there is no accepted approach to converting between all effect size statistics [215].

5.5 Concluding Remarks

In this chapter, the author demonstrated the calculation of standardised effect sizes for risk factors related to poor outcomes when patients are discharge from hospital. Whilst individual effect sizes are often small, there is substantial variability between different risk factors, patient cohorts and outcomes. The use of standardised effect sizes allows the easier comparison between such groups, this in turn may facilitate the development of better risk stratification models and risk minimisation interventions. We hope that, as a consequence of this work, more studies will look to calculate standardised effect sizes when considering risk factors, generating more directly comparable results and enabling more rapid translation into changes to patient care.

Chapter 6: Impact of Socioeconomic Geography on Outcomes at Hospital Discharge for People with Diabetes

6.1 Introduction

Chapter 5 considers risk factors, related to commonly extracted variables, associating to readmission and mortality for people with diabetes. These variables were informed from the systematic reviews in Chapters 3 and 4. Both these reviews, however, identified a potentially important role for socioeconomic variables related to outcomes, following discharge from hospital. This Chapter considers such socioeconomic variables in more detail. There are varying definitions of socioeconomic status, with one of the earliest being by Chapin in 1928, who defined socioeconomic status as “the position that an individual or family occupies with reference to the prevailing average of standards of cultural possessions, effective income, material possessions, and participation in group activity in the community” [222]. One of the key reasons for variations, in this baseline definition, is the wide range of different academic disciplines that consider socio-economic status as an important factor in their research. Sociologists, psychologists, medical researchers, educational researchers and many more all find the concept of socioeconomic status an important construct within their own disciplines [223].

Whilst there are variations in the exact definition of socioeconomic status, there are clear and widely reported associations between socioeconomic status and health outcomes [224, 225]. These cross physical, mental and emotional health outcomes [226, 227]. Naturally, for the purposes of this PhD we focus on the interactions between socioeconomic status and physical health. However, the complex interactions between physical, mental and emotional health should not be overlooked. The driver of varying health outcomes, related to socioeconomic status, is felt to be threefold.

Firstly, socioeconomic status has a direct impact on the ability of individuals to purchase or acquire resources and treatments that promote health. This can include factors impacting health directly, such as the ability to purchase medication [228], or more indirect influencers such as living in environments with less pollution [229] or more access to health promoting leisure activities [230].

The second driver of health outcomes, in relation to socioeconomic status, can be described as variations in the “socialization” of health influencing habits and activities and then the continued [231], and perhaps compounding socialization of health influencing habits and activities. This differs from the first driver in that it goes well beyond simple purchasing power but deeper into personal preferences and cultural habits between different groups. It is important to note that these habits can vary across different socioeconomic groups over time and be health promoting (such as exercise [232]) or health harming (such as smoking [233] or alcohol consumption [234]). This second driver is perhaps the most important driver for public health and state based interventions, as illustrated, for example, by minimal alcohol pricing [235, 236] or smoking bans [237].

The final driver is arguably the most interesting, in that it has been proposed, with good supporting evidence, that in addition to socioeconomic status driving health outcomes, health itself can driver socioeconomic status [238]. For example, people who are less healthy may miss more school education or have lower income through more missed days from work and increased difficulty acquiring a job. This driver acts directly at the “person” level but also has an indirect influence on family members, in particular where informal and unpaid caring elements are considered. Importantly, however, there may also be a direct influence of one person’s health affecting their socioeconomic status and that in turn also affecting the health & socioeconomic status of another individual through the epigenetic phenomenon of imprinting whereby a parent’s status impacts the genetic imprinting of their offspring [239].

These drivers are equally thought to apply to the context of diabetes, where there is a long established literature considering the impact of socioeconomic factors on outcomes. This association in diabetes was first reported in 1982, in relation to the incidence of diabetes associated with geographic deprivation, prospectively analysed in nine British Towns, with a particularly strong association noted for Type 2 diabetes [240]. This was followed by abundant research considering impact of socioeconomic status on the incidence of diabetes in varying demographic cohorts internationally [241, 242]. Importantly, there has also been significant research considering the dual impact of socioeconomic status and race on diabetes incidence [243].

Subsequent research considered the impact of socioeconomic status on control of diabetes, as well as the development of diabetes related complications in cohorts of patient with both Type 1 and Type 2 diabetes [244]. Lower markers of socioeconomic status have been associated with an increased T2DM prevalence [245], lesser attainment of diabetes treatment goals [246] and increased mortality [247]. Certain complications of diabetes, in particular diabetic foot disease have noted to be very strongly associated with socioeconomic status and deprivation [248, 249].

There has been much less research considering the impact of socioeconomic status on patient outcomes, in relation to in-hospital outcomes, for patients with diabetes. It is conceivable that this is due to a perception that the hospital environment reduces the impact of variations in socioeconomic status. The initial systematic reviews in chapters 3 and 4 [9] did, however, report that a relatively small number of studies considered the impact of socio-economic status on readmission rate, particularly for a small subsets of patients with type 1 diabetes [144]. The performed studies focused much more on the impact of socioeconomic status on readmission rather than the impact of socioeconomic status on mortality. The contrast between socioeconomic research for diabetes, in general, compared to research considering risk factors for patients with diabetes, at hospital discharge, may reflect the data interoperability challenges associated with matching diverse inpatient electronic health record (EHR), primary care and socio-economic datasets at the individual patient level.

To understand the impact of socioeconomic status on health outcomes, it is necessary to find a reliable source of socioeconomic data. Collecting information from individual patients is laborious and prone to potential bias. This would not support the wider ambition of this PhD of identifying risk through a health informatics approach. In the United Kingdom, the UK Census provides a "treasure trove of information about UK society," with a core function to provide a "to provide a (near) comprehensive snapshot of the UK population once a decade [250]."

In this Chapter, the author presents the first assessment of the impact of socioeconomic status on the risk of readmission and mortality, at the point of discharge from hospital for people with diabetes. The research approach combines electronic health record data with geographic socioeconomic data, based on postcode sectors.

The research utilises census data, published in the United Kingdom. In particular, the indices of multiple deprivation that are collected.

This research is essential if we are to personalise healthcare services to meet the needs of individual patients and appropriately design strategies to reduce the excess readmission and mortality risks seen for patients with diabetes when discharged from hospital.

6.2 Methods

The author performed a retrospective evaluation of data extracted from an electronic health record (EHR) of a large tertiary referral centre in the Coventry & Warwickshire region of the United Kingdom, for all patients discharged from with a diagnosis of diabetes, over a 3-year period. Outcome variable data were extracted for hospital readmission within 30 days and mortality within 180 days of hospital discharge.

The diagnosis of diabetes was taken from the coding of patients at discharge and, thus, if there was a discrepancy in the diagnosis within the record, the latest diagnosis of diabetes at discharge was used. Maternity patients were excluded from the study, due to the differing nature of maternity care and readmission patterns. Patients, discharged within the last 6 months of the study period, were not evaluated as index patients, to ensure that all patients had a full period of 6 months follow up on the electronic health record, in order to assess for the outcome measures of interest. Patients were cohorted into those with a recorded diagnosis of Type 1 diabetes and those with a diagnosis of type 2 diabetes. Patients with a postcode outside the Coventry & Warwickshire Region were excluded, this is because there is an increased risk that these patients may have attended UHCW for one admission, but subsequently been readmitted to another hospital (for which we do not have data collected). This process therefore helps ensure the accurate capture of readmission rates to the hospital.

Socioeconomic data was extracted from the latest UK Census, performed by the Office for National Statistics (ONS), this data was not available directly from the EHR. The last UK Census was performed in 2011 and published in July 2012, it represents a “detailed snapshot of the population and its characteristics, and underpin funding

allocation to provide public services," with a 93% coverage rate it is an unique an invaluable resource, considering the characteristics of the UK population

Socio-economic data was extracted from the ONS Nomis Portal relating to the following pre-specified variables; indices of multiple deprivation (the official measure of relative deprivation in England [251]), adults in employment, ethnicity, language, housing density, activity limitation and provision of unpaid care. Socio-economic data was extracted and matched to patient postcodes within the EHR at postcode sector level. The 5 digit postcode sector (eg "SW1A 2" from the full postcode "SW1A 2AA") represents the smallest area level within the Census dataset [252]. There are 89 postcode sectors, within the Coventry and Warwickshire region, with approximately 9000 people living in each postcode sector.

The association, between socioeconomic status and outcomes of interest, was assessed using Student's T Test for continuous variables, following adequate assessment for skew and kurtosis to ensure normality. An absolute skew value larger than 2 or an absolute kurtosis (proper), larger than 7, was used as reference value for determining substantial non-normality [219].

A p-value of <0.05 was considered significant. Standardised effect size was evaluated using Cohen's D for continuous variables. This allows comparison between the different markers of socioeconomic status, extracted from the UK Census data, and across the different cohorts of patients assessed.

All statistical testing was performed using Microsoft Excel 2016 [220] and IBM's SPSS v24 [221].

6.3 Results

Data were extracted for 24107 hospital discharges with a diagnosis of diabetes recorded, 2222 for patients with T1DM and 23365 for patients with T2DM. Twenty-three percent (N=5,659) of emergency hospital admissions resulted in readmission within 30 days for the generalised population of diabetes, with 30.5% (n=678) of emergency admissions with T1DM resulting in readmission within 30 days and 21.3% (n=4981) of emergency admissions with T2DM being readmitted within 30 days.

Fifteen percent of patients (n=3719) died within 180 days of hospital discharge in the generalised population of patients with diabetes, with 7.8% (n=175) of patients with T1DM and 15% (n=3460) of patients with T2DM dying within 180 days of hospital discharge.

Socioeconomic status was significantly associated with 1 of 19 variables for 30 days readmission in T2DM patient cohorts compared to 9 statistically significant variables for T1DM cohorts ($p<0.05$ Student's T test). Standardised size measures were relatively large and strongest for deprivation indices (Cohen's D 0.29) and health related activity impairment (Cohen's D 0.15).

There was no statistically significant association between mortality and socioeconomic variables in the T1DM cohort. Socioeconomic status was statistically significantly associated with 14 of 19 socioeconomic variables, in relation to 180d mortality for the T2DM patient cohort ($p<0.05$ Student's T test). Standardised effect sizes were relatively small, however strongest for language and activity limitation (both 0.09).

Tables 18 and 19 present the association between socioeconomic factors and readmission at 30 days or mortality at 30 days for generalised populations of patients with diabetes, T1DM populations and T2DM populations at discharge from hospital. A standardised effect size measure (Cohen's D) is presented for statistically significant associations.

	Readmission all diabetes		Readmission T1DM		Readmission T2DM	
	TTEST	Cohen's D	TTEST	Cohen's D	TTEST	Cohen's D
% not deprived	0.75		0.00	0.14	0.25	
% deprived in 1 dimension	0.16		0.00	-0.29	0.33	
% deprived in 2 dimensions	0.72		0.09		0.20	
% deprived in 3 dimensions	0.54		0.01	-0.12	0.41	
% deprived in 4 dimensions	0.50		0.03	-0.10	0.51	
% Adults in employment	0.71		0.11		0.19	
% Ethnic minority race (Not English)	0.05	0.03	0.01	0.13	0.17	
Day-to-day activities limited a little %	0.01	0.04	0.00	0.16	0.12	
Day-to-day activities limited a lot %	0.03	0.03	0.05	0.09	0.10	
Day-to-day activities not limited %	0.01	-0.04	0.00	-0.14	0.08	
Day-to-day activities limited a lot: Age 16 to 64 %	0.04	0.03	0.14		0.08	
Day-to-day activities limited a little: Age 16 to 64 %	0.18		0.95		0.11	
Day-to-day activities not limited: Age 16 to 64 %	0.04	-0.03	0.63		0.05	
Provides no unpaid care %	0.49		0.36		0.44	
Provides 1 to 19 hours unpaid care a week %	0.86		0.28		0.92	
Provides 20 to 49 hours unpaid care a week %	0.27		0.46		0.13	
Provides 50 or more hours unpaid care a week %	0.06		0.41		0.09	
Main language is not English	0.00	0.05	0.02	0.11	0.00	0.05
Density (number of persons per hectare)	0.93		0.14		0.43	

Table 17: Association between socioeconomic status and readmission risk at 30 days (red is not statistically significant, green is statistically significant at p<0.05)

	Mortality all diabetes		Mortality T1DM		Mortality T2DM	
	TTEST	Cohen's D	TTEST	Cohen's D	TTEST	Cohen's D
% not deprived	0.17		0.49		0.00	-0.08
% deprived in 1 dimension	0.12		0.24		0.01	0.05
% deprived in 2 dimensions	0.14		0.84		0.00	0.07
% deprived in 3 dimensions	0.03	0.04	0.36		0.00	0.08
% deprived in 4 dimensions	0.02	0.04	0.25		0.00	0.08
% Adults in employment	0.50		0.74		0.02	0.04
% Ethnic minority race (Not English)	0.00	0.05	0.07		0.00	0.09
Day-to-day activities limited a little %	0.29		0.57		0.95	
Day-to-day activities limited a lot %	0.00	-0.08	0.69		0.01	-0.05
Day-to-day activities not limited %	0.01	0.05	0.61		0.25	
Day-to-day activities limited a lot: Age 16 to 64 %	0.04	0.04	0.38		0.00	0.05
Day-to-day activities limited a little: Age 16 to 64 %	0.23		0.80		0.01	0.05
Day-to-day activities not limited: Age 16 to 64 %	0.00	0.06	0.72		0.15	
Provides no unpaid care %	0.01	0.05	0.37		0.03	0.04
Provides 1 to 19 hours unpaid care a week %	0.02	-0.04	0.34		0.01	-0.05
Provides 20 to 49 hours unpaid care a week %	0.78		0.76		0.01	0.05
Provides 50 or more hours unpaid care a week %	0.23		0.76		0.96	
Main language is not English	0.01	0.04	0.05		0.00	0.09
Density (number of persons per hectare)	0.19		0.87		0.12	

Table 18: Association between socioeconomic status and mortality risk at 180 days

6.4 Discussion

There is a strong association between geographic socio-economic status and readmission outcomes for patients with T1DM. However, there is very limited association between socio-economic status and mortality outcomes for the T1DM cohort. In direct contrast, socioeconomic status is strongly associated with mortality outcomes, following hospital discharge, for patients with T2DM, whilst there is very little association with readmission.

This is an important finding, as it will help guide and understanding of how to most appropriately risk stratify these different patient cohorts at discharge from hospital, as well as make suggestions as to the potential design of interventions to reduce readmission or mortality following discharge. The results also go some way to explaining variations in outcomes, when patients are discharged from hospital with diabetes, as it suggests that both the geographic socioeconomic status and the type of diabetes may be of significant relevance.

These results clearly demonstrate an association between geographic socioeconomic status and outcomes, following hospital discharge. However, they do not provide any information on causation. Further work is clearly needed to understand the possible mechanisms for the findings reported here. In particular, we have not attempted to control the populations for factors such as age, sex or diabetes control. Whilst we have not controlled for such variables, the results remain meaningful and useful, in particular in the development of risk stratification tools.

There are a number of both strengths and weaknesses with the study described. Foremost, amongst the strengths is that we have used a large sample size over a prolonged period of time (3 years). This is important as previously very few studies, which have looked at the association between socioeconomic status and diabetes outcomes, have utilised meaningful sample sizes [253]. We have however only considered a single centre in the study described, albeit a large tertiary referral centre, set within a diverse population representing a mix of affluence, ethnicity and urbanisation. This consideration of a single centre does mean that some readmission events may be missed, as patients may have been subsequently admitted to a

different hospital in the Coventry & Warwickshire region (for example George Eliot NHS Hospital in Nuneaton or South Warwickshire NHS Foundation Trust Hospital in Warwick). However, the risk of this is likely to be low, as those admitted via ambulance will typically be taken to the nearest hospital and patients tend to attend the same hospital where they receive most of their care. Arguably the impact may be highest for more affluent socioeconomic groups, who are likely to be more geographically mobile; for instance, with greater car ownership and longer work commutes meaning they are more likely to come within the catchments of different hospitals, during the follow-up period of the study. This limitation does not apply to mortality on the basis that date of deaths for patients within the electronic health record are extracted from General Practice records before being uploaded to the UHCW NHS Hospital Trust electronic health record. Therefore wherever patients die their death should be accurately coded within the UHCW EHR from which data has been extracted.

The use of postcode sectors, as opposed to full postcodes, also merits discussion. This was necessitated both by the availability of census data, provided within the ONS datasets, and the additional need to ensure that patient identity was not inadvertently compromised. From a research perspective, it would of course be interesting to repeat the analysis with identifiable patient datasets and full postcodes with an individual assessment of social-economic status. However, from a practical perspective the benefits of such an approach would be limited. The use of full postcodes would not allow more accurate information to be extracted from the census, as the census also reports at a geographic level rather than an individual postcode based level. Furthermore, the use of postcode sectors and publically available socio-economic datasets allows ready and rapid incorporation of such data into risk stratification tools, which could be implemented within hospital discharge processes without significant disruption to the clinical teams, and yet provide valuable information. A more detailed understanding could be achieved through a sociological based approach of assessing each individual's socioeconomic status directly at discharge from hospital, through a survey or interview based approach. Such an individual assessment of socio-economic status, at discharge, would of course be rather laborious and could not be practically incorporated into a risk stratification tool capable of delivering point-of-care information to clinicians, when discharging patients with diabetes from hospital.

There are other limitations in considering the use of census based research. The first of these is that the last census was performed in 2011, making it now 9 years old. Whilst there has been relatively little geographic change in the population of the Coventry & Warwickshire region, there has been significant gentrification of the city centre area, and rapid increases in student populations in other areas. It is conceivable, therefore, that the socio-economic status of some postcode sectors may have changed since the census was completed and therefore not be representative of the current population. The next UK Census is not planned until 2021 [254], with the publication of census results typically taking a further 12 months. Given there is no other reliable source of geographic socioeconomic based information, there is little alternative option but to use existing census data, the vast majority of which is likely to be representative of the patient population.

This research only considered the post-discharge outcomes of patients with type 1 and type 2 diabetes. An important cohort that was not considered are pregnant ladies with a diagnosis of either type 1, type 2 or gestational diabetes being discharged following delivery. Pregnant ladies with a diagnosis of diabetes are counselled to deliver in hospital and this is essential for those on insulin replacement. The post-discharge outcomes for this cohort of patients would perhaps need to be extended beyond readmission or mortality, in order to consider both important maternal and paediatric outcomes. Understanding the socio-economic impact of socioeconomic status on diabetes control, delivery and post-delivery outcomes is particularly important given the potential to have a direct impact on both the mother and the future lifespan of the recently born child. This builds on the increasing evidence around the impact of the maternal uterine environment on future diabetes and obesity risk in the offspring [255]. There is potential, therefore, that this could act as a mechanism of compounding socio-economic driven health inequality across generations and should therefore be an important target for future research. Indeed, we are currently developing a research collaboration between University Hospitals Coventry & Warwickshire NHS Trust & The Institute of Digital Healthcare that assesses post discharge factors relating the maternal mental health outcomes. Based on the results discussed in this chapter, the author would suggest that an inclusion of socio-economic factors should be incorporated within the research approach.

6.5 Concluding Remarks

In summary, we present here the first large scale assessment of the impact of geographical socio-economic status, collected from publically available data sources on outcomes for cohorts of patients, discharged from hospital with diabetes. We demonstrate clear associations between socio-economic status and readmission for patients with T1DM and socioeconomic status and mortality for patients with T2DM. These findings can, and we believe should be readily incorporated into risks stratification tools applied at the point of discharge and thus supported evidence based individualised care for patients leaving hospital with diabetes. An important element, in the relationship between socioeconomic status and healthcare outcomes, is felt to be the impact of socioeconomic status on glycaemic control (or Hba1c). The impact of glycaemic control and discharge outcomes for patients with diabetes in considered in more detail in the next chapter.

Chapter 7: Association between glycosylated haemoglobin and patient outcomes

7.1 Introduction

Chapter 1 highlighted the underlying nature of diabetes as a condition of impaired glycaemic control [22]. Therefore, one of the central features of diabetes care aims to return glycaemic control into a physiological range through diet, oral medications or injectable medications [25, 30]. Glycaemic control is typically measured through either fingerpick blood sugar readings or in a laboratory blood test, termed glycosylated haemoglobin levels (Hba1c) [256]. Fingerprick blood sugar readings provide an immediate reading of the blood sugar level, at that point in time. Finger prick blood tests are typically taken on a hand-held device, either the patient's own or a healthcare organisation's. The glycosylated haemoglobin value (Hba1c) reports the amount of glucose bound to haemoglobin molecules, and represents an average of blood sugar control over the preceding 6 weeks prior to the test being taken [256]. Hba1c values are typically collected by a venous blood sample that is sent to a processing laboratory (although near-patient systems do exist [257]) and thus almost all such values are uploaded to electronic health record systems (unlike many finger-prick blood sugar samples).

There are not "normal values" for Hba1c in patients with diabetes, meaning there is no set range of Hba1c values we expect all patients to fall within if they are well controlled; rather these have to be individualised to each patient. The Hba1c value, however, can be used in both the diagnosis of T2DM and monitoring of all types diabetes (although less useful in monitoring GDM). An Hba1c of 48mmol/mol is deemed diagnostic of T2DM, whilst an Hba1c between 42 and 47 mmol/mol is diagnostic of impaired glucose regulation or a "prediabetes" state [258]. When monitoring control of diabetes using Hba1c it is typically the change in Hba1c value over time that is most useful rather than an individual Hba1c value. NICE generally recommend an Hba1c level target of 48 mmol/mol in treatment of T2DM, however, stress that this target must be personalised and should be relaxed to 53 mmol/mol where there is a risk of hypoglycaemia. Importantly, NICE recommend escalation of medication control where the Hba1c is in excess of 58mmol/mol [25].

There is good evidence that maintaining glycaemic levels within physiological levels (i.e. below the 48 mmol/mol diagnostic threshold described above) can reduce or minimise the risk of diabetic complications in the long term (months-years), both for

patients with T1DM and T1DM [32, 33]. Shorter-term blood sugar control also can have a significant impact on health outcomes, with significantly higher or lower readings resulting in significant morbidity, mortality and healthcare utilisation. Low blood sugars (below 4.0 mmol/L) cause the condition of hypoglycaemia, which can result in changes to conscious levels, seizures or even death [259]. Higher blood sugar values (above 11.0 mmol/L) can cause complications (such as thrombosis) through increased blood viscosity but, more worryingly, can also cause patients to develop diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic states (HHS). DKA can be defined as "an acute metabolic emergency occurring in individuals with absolute or relative insulin deficiency and is typically characterised by hyperglycaemia, ketonaemia and acidosis [260]." HHS, in contrast, is characterised by a high osmolality, high blood glucose level and severe dehydration [261]. Both DKA and HHS are associated with significant morbidity and mortality, and almost universally require hospital admission for intravenous insulin infusions [262, 263]. It is important to note that inter-current illnesses (such as ischaemic cardiac events, infection and trauma) or iatrogenic insults (such as surgery and chemo/radiotherapy) can generate a stress response within the body, resulting in excess cortisol generation and subsequent elevations in blood sugar readings. In contrast, patients who are on hypoglycaemic medications (including insulins and gliclazide tablets) may be at risk of hypoglycaemia, if they are unable to eat through nausea/vomiting or loss of appetite for other reasons [264].

Therefore, managing glycaemic control, in the context of inter-current illness and diabetes, is a relatively complex process. In particular, there has been significant research considering the optimal glycaemic for patients who are inpatients within hospital settings. There is a need to balance the risks of overly tight glycaemic control that risks hypoglycaemia versus the risks of thrombosis, DKA and HHS that can occur with higher blood sugar values. It has been identified that glycaemic control can impact on both survival and length of stay for people with diabetes, admitted to hospital [265]. Hyperglycaemia has clearly been associated with adverse patient outcomes across a number of studies [266, 267]. However, interventions that have aimed to correct blood sugars into normal ranges have either not improved outcomes [268, 269] or, in certain circumstances, lead to worsening outcomes [269]. Randomised controlled trials have suggested that hypoglycaemia is the primary driver of worsening patient outcomes,

associated with overly intense inpatient blood sugar control [270]. Therefore, the overall consensus and guideline driven position for inpatient glycaemic control is that, in general, inpatient populations a moderate, rather than overly tight control is advisable to optimise patient outcomes, including length of stay and readmission risk [271].

However, when considering the impact of glycaemic control on the discharge process from hospital, and associated risks of readmission or mortality, there has been much less research. Two articles consider the impact of glycaemic control, in general, on readmission; one of which focuses on the importance of the “most extreme blood sugar value” during inpatient admission and the second article considers the impact of glycaemic variability. Both articles therefore considered relatively specific markers of inpatient glycaemic control and both were restricted to specific subsets of hospital inpatients with diabetes [144, 148]. Importantly, however, there has been considerably more research looking at the impact of inpatient hypoglycaemia on readmission patterns for patients discharge from hospital with diabetes, with [129, 135, 136, 142]. These studies all considered generalised populations of people with diabetes admitted to hospital, rather than specific subsets of patients. It is likely that this focus, on hypoglycaemia and readmission patterns, is driven by an awareness of hypoglycaemia, as a major driver of hospital admission, and therefore cost in diabetes management. Thus, it is highly relevant to the previously discussed financial penalties associated with hospital readmission described in chapter 3 and 4. Remarkably, there is even less research considering the impact of glycaemic control on mortality outcomes following hospital discharge, with no relevant articles identified during the systematic review discussed in chapter 4.

This chapter looks to perform the first evaluation of the impact of glycaemic control on discharge outcomes of mortality and readmission, when patients with diabetes are discharged from hospital. It focuses on both the value of glycosylated haemoglobin and how soon monitoring is performed after discharge. The use of Hba1c is selected due to its ready availability in electronic health record systems, therefore facilitating an informatics based approach both in this research, but also when considering wider dissemination and adoption of this work in other settings.

7.2 Methods

The work, discussed in this chapter, adopted a similar retrospective evaluation of the EHR data extracted from University Hospitals Coventry and Warwickshire NHS Trust for patients discharged with a diagnosis of diabetes, over a 3-year period. Only adult patients with Type 1 or Type 2 diabetes were included. Patients with gestational diabetes were excluded from the research. This is particularly important for the work reported in this chapter, because Hba1c values vary significantly during pregnancy, with no clear normal ranges established [272]. Indeed, the National Institute of Health & Clinical Excellence do not recommend Hba1c measurement during pregnancy [273].

All Hba1c values for patients in the Coventry & Warwickshire region (including those performed in the community setting) are analysed at the hospital laboratory and included within the electronic health record. Patients performing Hba1c measurements on home devices were not included, however these are exceptionally rare indeed. Hba1c values were extracted for all patients discharged with diabetes, as above. Patients from outside the region may have had Hba1c values calculated at other hospital laboratories and whose readings would not appear on UHCW's Electronic Health Record. Therefore, patients who had postcode sectors outside of the Coventry & Warwickshire region were also excluded from the study. Extraction of data was supported by a biochemistry and Performance and Programme Management Office analyst.

The outcomes of interest explored through the systematic reviews in chapter 3 and 4 were readmission within 30 days and mortality within 365 days. Associations with these outcomes were calculated both for Hba1c tests, performed during the index admission period, and separately for Hba1c tests performed following discharge from hospital. The longer period used for considering mortality (chapters 5 and 6 of this thesis have considered mortality within 180 days) is based on the nature of Hba1c as a longer-term measure of diabetes control and therefore a longer outcome measure was felt appropriate. Associations were investigated for generalised populations of patients with diabetes and subpopulations diagnosed with both T1DM and T2DM. In addition to exploring associations between the Hba1c value and the above variables, supplementary analysis was performed to look for any association between the time

delay (in days) between discharge from hospital, for patients with diabetes, and the checking of an Hba1c value.

The association between Hba1c absolute values and frequency of Hba1c monitoring was analysed using Student's T Test, following adequate assessment for skew and kurtosis, in order to ensure normality. An absolute skew value larger than 2 or an absolute kurtosis value (proper) larger than 7 may be used as reference for determining substantial non-normality [219]. A p-value of <0.05 was considered significant. Standardised size was evaluated using Cohen's D for pre-specified patient cohorts of patients with Type 1 Diabetes and Patients with Type 2 diabetes. The "rules of thumb" established for interpreting Cohen's D values, in Chapter 5, continue to be appropriate for this chapter.

All statistical testing was performed using Microsoft Excel 2016 [220] and IBM's SPSS v24 [221].

7.3 Results

Hba1c during admission

There were 399 patients meeting the inclusion criteria described above, who had a Hba1c sample analysed and recorded in the electronic health record system, during their hospital admission prior to discharge. 52 of these patients were readmitted within 30 days and 63 died within 365 days. The mean average Hba1c value of this cohort overall was 73 mmol/mol.

Hba1c during admission – readmission (Table 20)

The mean average Hba1c during admission for patients who were not readmitted within 30 days was 74.6 mmol/mol, compared to 65.6 mmol/mol for patients readmitted within 30 days of discharge (p=0.006, Cohen's D 0.33).

Average Hba1c during admission	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
Not readmitted within 30 days	309	74.58	1.10	1.29
Readmitted within 30 days	52	65.62	1.78	3.98

P-value	0.0058
Cohen's D	0.33

Table 19: Association of Hba1c during admission with readmission (generalised population of patients with diabetes)

Hba1c during admission – mortality (Table 21)

The mean average Hba1c assessed during admission for patients who survived 365 days was 69.1 mmol/mol and the mean average Hba1c for patients who died within 365 days was 64.1 mmol/mol. (p=0.1, Cohen's D N/A).

Average Hba1c during admission	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
No death within 365 days	305	69.05	0.99	0.75
Died within 365 days	56	64.11	2.19	6.37

P-value	0.10
Cohen's D	0.21

Table 20: Association of Hba1c during admission with mortality (generalised population of patients with diabetes)

Hba1c post discharge

There were 3403 patients who had an Hba1c recorded in the electronic health record system following discharge from hospital with a diagnosis of diabetes. There were 3138 patients who had an Hba1c within a year of hospital discharge. For patients who had an Hba1c assessed within a year of hospital discharge the mean average Hba1c was 59.9 mmol/mol, with an average time until Hba1c assessment of 110 days.

Hba1c post discharge readmission

When considering absolute Hba1c values and readmission for generalised populations of patients with diabetes (n=3403), the average Hba1c value of those not readmitted to hospital within 30 days was 60.4 mmol/mol, whereas the average Hba1c of those readmitted to hospital was 57.8 mmol/mol (p=0.008, Cohen's D 0.28) (Table 22).

Average Hba1c post-discharge (All)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
Not readmitted within 30 days	2618	60.39	1.50	3.60
Readmitted within 30 days	520	57.82	1.75	4.15

P-value	0.0088
Cohen's D	0.28

Table 21: Association of Hba1c post-discharge with readmission (generalised population of patients with diabetes)

The average number of days to Hba1c testing, for those discharged from hospital and not readmitted, was 115.2, whereas the average number of days until testing for those discharged and then readmitted was 83.1 days. (p<0.001, Cohen's D 0.39) (Table 23).

Average time to hba1c post-discharge (All)	N	Average No. of days	Skew	Kurtosis
No. of days to test, no readmission within 30d	2618	115.23	0.80	-0.18
No. of days test , readmission within 30d	520	83.05	1.01	0.34

P-value	0.00006
Cohen's D	0.39

Table 22: Association between readmission and time to testing Hba1c (generalised population of people with diabetes)

For patients with type 1 diabetes, the average Hba1c for those not readmitted was 74.4 mmmol/mol, whereas the average Hba1c for those readmitted was 63.6 mmol/mol (p=0.0077, Cohen's D 0.44) (Table 24).

Average Hba1c post-discharge (T1DM)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
Not readmitted within 30 days	281	74.37	1.39	4.13
Readmitted within 30 days	42	63.64	0.86	0.35

P-value	0.0077
Cohen's D	0.44

Table 23: Association of Hba1c post-discharge with readmission (T1DM population)

The average number of days, between hospital discharge and the Hba1c being tested, was 109.4 for those readmitted and 114.9 for those not readmitted (p=0.72, Cohen's D N/A) (Table 25).

Average time to hba1c post-discharge (T1DM)	N	Average No. of days	Skew	Kurtosis
No. of days to test, no readmission within 30d	281	109.46	0.89	-0.21
No. of days to test, readmission within 30d	42	114.86	0.76	-0.54

P-value	0.72
Cohen's D	N/A

Table 24: Association between readmission and time to testing Hba1c (T1DM)

For patients with type 2 diabetes, the average Hba1c, for those not readmitted was 58.8 mmol/mol, whereas the average Hba1c, for those readmitted was 57.5 mmol/mol (p=0.19, Cohen's D N/A) (Table 26).

Average Hba1c post-discharge (T2DM)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
Not readmitted within 30 days	2246	58.83	1.45	2.59
Readmitted within 30 days	459	57.50	1.88	4.95

P-value	0.19
Cohen's D	N/A

Table 25: Association of Hba1c post-discharge with readmission (T2DM population)

The average number of days, between discharge and Hba1c being tested for those not readmitted, was 113.5 days, compared to 95.2 days for those readmitted (p<0.001, Cohen's D 0.33) (Table 27).

Average time to hba1c post-discharge (T2DM)	n	No. of days	Skew	Kurtosis
No. of days to test, no readmission within 30d	2246	113.50	0.80	-0.23
No. of days to test, readmission within 30d	459	95.23	1.05	0.50

P-value	0.00002
Cohen's D	0.33

Table 26: Association between readmission and time to testing Hba1c (T2DM)

Hba1c post discharge mortality

The average Hba1c for the generalised population of patients with diabetes, who were discharged and survived for over one year, was 60.2 mmol/mol, whereas the average Hba1c for those with mortality within 1 year was 56.7 mmol/mol (p=0.007, Cohen's D 0.18) (Table 28).

Average Hba1c post-discharge (All)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
No death within 365 days	2924	60.206	1.54	3.57
Died within 365 days	214	56.73	1.28	1.97

P-value	0.0074
Cohen's D	0.18

Table 27: Association of Hba1c post-discharge with mortality (generalised population of patients with diabetes

The mean average time to Hba1c testing, for those who survived over a year, was 112 days, whereas the mean average time to testing, for those with mortality within 1 year, was 83 days (p<0.001, Cohen's D 0.37) (Table 29).

Average time to hba1c post-discharge	n	No. of days	Skew	Kurtosis
No. of days to test, survived 365 days	2924	112.19	0.81	-0.21
No. of days to test, died within 365 days	214	83.33	1.17	0.93

P-value	<0.0001
Cohen's D	0.36

Table 28: Association between mortality and time to testing Hba1c (generalised population of people with diabetes)

For patients with type 1 diabetes, the average Hba1c, for those who survived to 365 days post discharge, was 73.2 mmmol/mol, whereas the average Hba1c, for those readmitted, was 59.4 mmol/mol (p<0.001, Cohen's D 0.78) (Table 30).

Average Hba1c post-discharge (T1DM)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
No death within 365 days	308	73.20	1.27	3.58
Died within 365 days	15	59.41	-0.26	-1.57

P-value	0.00023
Cohen's D	0.78

Table 29: Association of Hba1c post-discharge with mortality (T1DM population)

The average number of days, between hospital discharge and the Hba1c being tested, was 110.8 for those readmitted and 98.5 for those not readmitted (p=0.59, Cohen's D N/A) (Table 31).

Average time to hba1c post-discharge (T1DM)	n	No. of days	Skew	Kurtosis
No. of days to test, survived 365 days	308	110.89	0.87	-0.26
No. of days to test, died within 365 days	15	98.47	0.73	-0.70

P-value	0.59
Cohen's D	N/A

Table 30: Association between mortality and time to testing Hba1c (T1DM)

For patients with type 2 diabetes, the average Hba1c, for those who survived 365 days post discharge, was 58.3, whereas the average Hba1c for those who died within 365 days was 54.2 (p=0.07, Cohen's D N/A) (Table 32).

Average Hba1c post-discharge (T2DM)	n	Av Hba1c (mmol/mol)	Skew	Kurtosis
No death within 365 days	2513	58.30	1.54	3.08
Died within 365 days	192	54.18	1.31	2.01

P-value	0.07
Cohen's D	N/A

Table 31: Association of Hba1c post-discharge with mortality (T2DM population)

The average number of days between discharge and Hba1c being tested, for those not readmitted, was 113.5 days, compared to 96.119 days for those readmitted (p0>0.001) Cohen's D 0.21)(Table 33).

Average time to hba1c post-discharge (T2DM)	n	No. of days	Skew	Kurtosis
No. of days to test, survived 365 days	2513	113.53	0.80	-0.18
No. of days to test, died within 365 days	192	96.1	1.01	0.34

P-value	<0.0001
Cohen's D	0.21

Table 32: Association between mortality and time to testing Hba1c (T2DM)

7.4 Discussion

The measurement of Hba1c, in patients with diabetes, has been a mainstay of monitoring disease and the long-term, future microvascular and microvascular risk since the Diabetes control and complications trial (DCCT) and UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes (UKPDS) published their results [32, 35]. In both these studies, increased Hba1c values are associated with higher levels of adverse outcomes within the patient populations. In this chapter, a first evaluation of the association, between glycaemic control on discharge outcomes of mortality and readmission when patients with diabetes are discharged from hospital, is presented.

The results demonstrated no statistically significant associations between the Hba1c values, recorded during the inpatient stay, for both readmission and mortality outcomes. It is important to note that the population size was relatively small (361 patients) for each and may, thus, contribute towards the results not reaching significance. This small population size is notable, in that it potentially reflects a large proportion of patients with diabetes attending hospital, but not having their Hba1c assessed during the admission period. This does not necessarily mean that clinical teams were not conscious of the Hba1c measure, when seeing these patients, but they may note the most recent Hba1c, previously collected in the community setting. Additionally, the Hba1c values typically take the laboratory, at UHCW, 24 hours to process; therefore, this delay may mean for short admission patients clinical teams feel there is less need to request an Hba1c value.

However, statistically significant associations were noted in relation to Hba1c values following discharge from hospital. The Hba1c value is statistically significantly associated with 30-day readmission and 365-day mortality, in generalised populations of patients with diabetes. The Hba1c is statistically significantly associated with readmission and mortality for T1DM cohorts, but not this was not seen for T2DM cohorts. Importantly, for both the generalised population of patients with diabetes and the T1DM cohorts, it was a higher Hba1c that was associated with lower rates of mortality and readmission. This may seem counterintuitive; however, similar patterns were seen in inpatient studies, based on finger-prick based glucose readings. In these studies, higher blood sugar readings were protective [274]. This was explained by the

high risks of negative outcomes associated with hypoglycaemia, resulting from overly tight glycaemic control. It is likely that similar patterns may be being observed here, with hypoglycaemia already known to be a major driver of hospital readmission [275] and mortality [276]. It is possible that T2DM patients, who are on insulin or gliclazide and T1DM (who are all on insulin) are the drivers of the results observed here, for both the generalised population of patients with diabetes and T1DM cohort. The high number of T2DM patients, who are not on hypoglycaemia inducing medications, may explain the lack of significance in this subpopulation. The medications patients are on is not extractable from the electronic patient record system used at UHCW NHS Trust and the source of data for this research study. However, this is potentially an important observation and focus of future work.

The time, between discharge and the next testing of Hba1c values, was statistically significantly associated with both readmission and mortality, for generalised populations of patients with diabetes. The time, between discharge and testing, was not significantly associated with mortality or readmission for patients with T1DM; however, it was significantly associated with patients with T2DM. The pattern for the generalised diabetes cohort and T2DM cohort follows what would be anticipated, with negative outcomes associated with a shorter period to Hba1c measurement. This likely represents more frequent contact with medical team for patients with diabetes, who are more likely to experience negative outcomes, and these medical teams requesting Hba1c more frequently. The lack of statistically significant association for patients with T1DM may be explained either by the smaller sample size, or perhaps, more likely, by the more frequent contact these populations have with medical teams as a routine part of their care, regardless of their underlying risks. Indeed, nearly all T1DM are seen in secondary care hospital clinics, as opposed to T2DM cohorts, who are managed in the community and, although meant to have an at least annual nurse review with Hba1c, they have significantly less contact with medical teams.

This research work, presented in this chapter, has a number of limitations. There is the potential for missing values and missing data. The number of Hba1c tests, performed during the inpatient admission period, is perhaps lower than expected. However, the extraction process was supported by a Biochemistry Analyst at UHCW and, therefore, likely reflects a full and complete dataset, as contained within the clinical system. Any informatics based project risks issues with data availability and

missing values and it would be important to repeat this research at other centres, in order to look for differences in the outcomes generated.

Secondly, Hba1c values themselves can, to some extent, be unreliable, primarily influenced by factors affecting the lifespan of a patient's erythrocytes [277]. Whilst, for the vast majority of patients being discharged from hospital, they are likely to represent a good marker of recent glycaemic control, in some circumstances they can be misleading. Reasons for non-representative Hba1c values can include; blood transfusions [278], pregnancy [272], sickle cell disease [279], medications [280] and dialysis [281]. The most important of these perhaps being the impact of blood transfusions in patients discharged following surgery, trauma or gastrointestinal bleeding, where large volumes of blood may have been transfused.

This thesis chapter differs from previous chapters in being more exploratory in nature. Whilst the other chapters suggest factors that could readily be incorporated into risk prediction for patients leaving hospital with diabetes, the influence of Hba1c is less clear. Indeed, much of the data that this chapter focuses on considers risk factors following discharge; unlike previous chapters that focus on risk factors that are identifiable during the hospital admission period. This work is nevertheless important in demonstrating that biochemistry data may have an important role in understanding risk for patients with diabetes. This is also highly relevant as new technologies may allow earlier identification of patterns, which have been suggested by the Hba1c results collected here. Hba1c retrospectively looks at glucose patterns over the previous 6-week period, acting as an average effect rather than simple "point-in-time" blood sugar readings, which are entirely dependent on when the blood sugar reading is actually performed (in hospital, for example, the majority of fingerpick testing may be done around acute decompensations or surgical interventions, during the inpatient procedure, thus giving a non-representative summary of the overall blood sugar profile. We are, however, now able to gain better understanding of average blood sugar readings through continuous blood sugar monitoring systems (CGM) [282] or interstitial fluid blood sugar monitoring systems, such as the Freestyle Libre [283]. Data from these systems are not widely available, in relation to inpatient care and the immediate post discharge period. However, the research presented here suggests that such information may be of significant importance, in better understanding the risks when patients with diabetes are discharged from hospital.

Finally, this chapter stresses that the hospital discharge process is a continuum, not just a point in time, with Hba1c values stretching across that continuum. This is a particularly important observation, as this was a feature stressed during the patient public involvement work, at the start of this PhD thesis, and something that clinicians often forget. The discussion chapter describes, in more detail, how this thesis can form the basis of risk prediction modelling, at the point of discharge from hospital, and a challenge will be considering how prediction algorithms can be responsive to both data collected during the hospital admission itself and the post discharge period.

7.5 Concluding Remarks

Glycaemic control is currently the main indicator of effective diabetes management; typically, this is assessed through Hba1c values. This chapter creates new knowledge in demonstrating the association between glycaemic control, in the post discharge period, and negative outcomes of readmission and mortality both for generalised and specific subpopulations of diabetes. Importantly, this research extends current understanding from glycaemic control in the inpatient setting, in that low Hba1c's measurements may be associated with worse outcomes following hospital discharge, particularly for cohorts of patients with T1DM. This research represents an exploratory chapter identifying the need for further research to characterise the "peri-discharge" period from a glycaemic perspective. Newer technologies may enable a more detailed understanding of how glycaemic control varies around the time of hospital discharge and its subsequent influence on patient outcomes and thus could form the foundation of important future grant applications, publications and high-impact research.

Chapter 8: Discussion & Conclusion

8.1 Introduction

Diabetes is known to be a data-rich pathology, with a wealth of readily extractable data available on clinical electronic patient record systems [6]. Diabetes also represents a significant challenge to modern healthcare services, given the increasing prevalence of diabetes as a disease [284], and the increasing complexity/cost of managing both diabetes itself and subsequent complications [285]. Whilst significant research has been conducted to guide understanding of diabetes care in both the community setting and in the hospital inpatient setting, much less research has considered that key transition point from hospital to community care, when a patient with diabetes is discharged from hospital [9]. The patient and public involvement (PPI) work, described at the start of this thesis, demonstrated very clearly that this transition point is considered to be vitally important to people with diabetes and their carers. However, the transition is often neglected by the clinical teams who care for such patients. Clinicians are more likely to see hospital discharge as a point-in-time, the end-point of hospital admission, whereas patients, and their carers, see this as a process in itself, with risks and quality measures associated to the discharge processes rather than to the admissions process as a whole. The increased availability of data from electronic patient record systems, for the first time, allows us to better delineate and understand that discharge process and factors associated with it.

This thesis is based around better understanding the association between potential risk factors and the negative outcomes of hospital readmission and mortality for patients with diabetes. The research is founded within the existing research literature, by comparing and contrasting two comprehensive literature reviews. The research then goes on to generate new knowledge directly from extracted electronic patient record data that may be used to support the development of better understanding and processes around hospital discharge, as well as forming the starting point for a number of new and exciting research proposals that span across both medical and data science based research.

This discussion chapter explores the results of the research described so far in this thesis in more detail, whilst highlighting the learning and new knowledge generated as

a consequence. The strengths and weaknesses of the approach are considered in detail, alongside a consideration of potential next steps for this research.

8.2 Results Summary

The initial systematic in Chapter 3 review identified 82 studies, which met the inclusion criteria for papers considering risk factors for readmission when patients with diabetes are discharged from hospital. Only 47 of these studies identified statistically significant risk factors associated with hospital readmission. When combining these studies, there are 72 distinct risk factors identified, either for generalised populations of people with diabetes or for specific cohorts of people with diabetes. The risk factors could be broadly grouped into the following categories: demographics, socioeconomic status, lifestyle, patient medical factors, inpatient stay factors, medication related or laboratory results. There was, however, a strong bias towards studies from the United States, which were typically based on retrospective data collected from US healthcare models, incorporating the US approach to hospital discharge and diabetes care. It is important to note that these approaches differ significantly from care models in the United Kingdom and other areas of Europe.

The systematic review for readmission risk was then compared with a systematic review considering risk factors associated with mortality, when patients with diabetes are discharged from hospital in Chapter 4. There has been much less research considering this area, with only 27 articles identified, of which 17 identified statistically significant. These risk factors could be grouped into similar categories (demographics, socioeconomic status, lifestyle, patient medical factors, inpatient stay factors, medication related or laboratory results) and again were based either on generalised populations of people with diabetes or specific cohort (for example, patients with type 1 diabetes). Importantly, in this systematic review there was an additional category identified, which was glycaemic control. This was different to the laboratory blood tests identified in the readmission systematic review.

These two systematic reviews in Chapter 3 & 4 identified an existing body of research that considers factors associated with negative outcomes, when patients with diabetes are discharged from hospital. This provided a solid foundation for the subsequent research performed, including the precedence and potential value of analysing both generalised populations of people with diabetes and more specific cohorts of diabetes (most commonly T1DM and T2DM). What was noticed, in the systematic reviews, was that typically there was significant underlying variation in the patient populations

described (both in the generalised patient populations and specific patient populations), alongside with significant variation in the definition of readmission or mortality and use of non-standardised effect size statistical tools. The latter precludes a meaningful quantitative comparison or meta-analysis of the effect sizes described, in order to create a “hierarchy” of risk factors, or to assess the consistency across studies identifying the same risk factors. This is compounded by the use of anonymised, retrospectively collected data that, due to ethical approvals and the risk of inadvertent patient identification, are not included in the appendices of the published papers. This means that it would be very difficult to use the existing research literature, as reported in these systematic reviews, to form the basis of a future, properly pre-specified risk prediction model.

The subsequent PhD chapter, Chapter 5, then, outlines and demonstrates the calculation of standardised effect size measures for risk factors, associated with readmission and mortality for patients with diabetes. The research is based on data that were extracted from the electronic health record of a major tertiary referral centre, over a 3-year period, for all patients discharged from hospital with a concurrent diagnosis of diabetes mellitus. Data were analysed for an exemplar set of 10 pre-specified risk factor variables. These variables were selected based on both pre-specification from the published research literature reviews, described earlier, and the ease of which data for these variables can be extracted from inpatient electronic health records. Ease of extraction was considered to ensure the results are generalizable to other healthcare organisations, internationally. The chapter successfully demonstrated the use of Cohen’s-D and Phi standardised effect size statistics. Effect sizes were noted to be larger for mortality compared to readmission, as well as for being larger for surgical and Type 1 diabetes cohorts of patients.

Whilst Chapter 5 explored risk factors that featured in a large number of the articles identified within the initial systematic review, Chapter 6 considers the impact of socio-economic geography, in more detail. The work discussed there quite significantly extends the small amount of literature on the subject, in relation to discharge of people from hospital with a diagnosis of diabetes. Chapter 6 identified that socioeconomic status was statistically significantly associated with 14 of 19 socioeconomic variables in relation to 180 day mortality for the T2DM patient cohort, with no statistically significant association between mortality and socioeconomic variables in the T1DM

cohort. Socioeconomic status was significantly associated with 1 of 19 variables for 28 day readmission in T2DM patient cohorts compared to 9 statistically significant variables for T1DM cohorts. Effect sizes were strongest for deprivation indices (Cohen's D 0.29) and health related activity impairment (0.15). The work, in effect, suggests that there is an association between the socioeconomic geography of where you live and your risk of mortality, following hospital discharge if you have T2DM. Whereas, if you have T1DM, the association is between the socioeconomic geography of where you live and your risk of readmission.

The final experimental chapter (Chapter 7) is more exploratory, considering the impact of glycated haemoglobin on the outcomes of interest. It works towards the aforementioned discussion of the discharge process as a continuum, with the impact of Hba1c both before and after discharge considered. The chapter identifies that lower Hba1c values, following discharge from hospital, are significantly associated with increased risk of readmission, as is a shorter duration until testing, with similar patterns observed for mortality. The findings were particularly prominent for cohorts of patients with T1DM. This chapter paves the way for further research, considering the impact on glycaemic control on discharge outcomes for patients leaving hospital with diabetes. Such research will become more feasible once newer technologies (such as continuous glucose monitoring or closed loop systems) are more fully adopted into both inpatient and community care.

An important element of this PhD is that the experimental chapters all use standardised effect size measures, allowing ready comparison between the different variables of interest (both dependent and outcome variables). This is significantly different to any of the articles identified during the systematic reviews. It is, therefore, an important source of new knowledge generated from this thesis. The collated effect size outcome measures are presented below. Only those associations found to be statistically significant are included. It is important to distinguish between the categorical Phi effect size measures and continuous Cohen's D effect size measures, as these, unfortunately, cannot be compared directly. They cannot be directly compared due to variations in the established "rules of thumb" for Phi or Cohen's D measures for their interpretation. Whilst some processes to enable conversion between effect size statistics have been published, there is no accepted approach to converting between all effect size statistics [215].

	Statistical Test	All diabetes discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	Cohens D	0.08		0.16			0.45			
Sex	Phi	-0.01	-0.01				-0.10		0.07	
Co-morbidity burden	Cohens D	-0.18	-0.11	-0.37		-0.12	0.39	-0.17		-0.18
Previous DKA	Phi	-0.10	-0.03	-0.10	-0.08		-0.17			
Dementia	Phi	0.03	0.03	0.01		0.03				0.06
DSN review	Phi	-0.03	0.04	0.02		0.07			-0.11	0.12
T1DM	Phi	-0.06	-0.03	-0.05	-0.06	-0.02	NA	NA	NA	NA
T2DM patients	Phi	0.02		0.03						
Unknown diabetes type	Phi	0.03	0.03	0.03		0.03				
Weekend Discharged	Phi	-0.01		0.03	0.05	-0.03		0.04		

Table 33: Assessment of standardised effect size between risk factors and readmission at 30 days

	Statistical Test	All diabetes discharges	Emergency admission discharges	Elective admission discharges	Emergency admission surgical discharges	Emergency admission medical discharges	T1DM Surgical patients	T2DM Surgical patients	T1DM Medical patients	T2DM Medical patients
Age	Cohens D	-0.76	-0.72	-0.45	-0.89	-0.70	-1.40	-0.79	-1.69	-0.56
Sex	Phi	-0.03	-0.03	-0.03	-0.03	-0.03				-0.03
Co-morbidity burden	Cohens D	-0.72	-0.64	-0.53	-0.90	-0.60	-0.86	-0.87	-1.41	-0.48
Previous DKA	Phi	0.05	0.08	0.03		0.09	0.13	0.01	0.23	0.03
Dementia	Phi	-0.06	-0.05		-0.04	-0.05	-0.16	-0.05	-0.09	-0.04
DSN review	Phi	-0.04	0.02	-0.02	-0.04	0.05			0.16	
T1DM	Phi	0.04	0.09			0.09	NA	NA	NA	NA
T2DM patients	Phi	-0.07	-0.08	-0.02	-0.10	-0.08				
Unknown diabetes type	Phi			0.02						
Weekend Discharged	Phi	-0.02	<0.01	0.02	-0.03	-0.04				-0.04

Table 34: Assessment of standardised effect size between risk factors and mortality at 180 days

	Readmission all diabetes		Readmission T1DM		Readmission T2DM	
	TTEST	Cohen's D	TTEST	Cohen's D	TTEST	Cohen's D
% not deprived	0.75		0.00	0.14	0.25	
% deprived in 1 dimension	0.16		0.00	-0.29	0.33	
% deprived in 2 dimensions	0.72		0.09		0.20	
% deprived in 3 dimensions	0.54		0.01	-0.12	0.41	
% deprived in 4 dimensions	0.50		0.03	-0.10	0.51	
% Adults in employment	0.71		0.11		0.19	
% Ethnic minority race (Not English)	0.05	0.03	0.01	0.13	0.17	
Day-to-day activities limited a little %	0.01	0.04	0.00	0.16	0.12	
Day-to-day activities limited a lot %	0.03	0.03	0.05	0.09	0.10	
Day-to-day activities not limited %	0.01	-0.04	0.00	-0.14	0.08	
Day-to-day activities limited a lot: Age 16 to 64 %	0.04	0.03	0.14		0.08	
Day-to-day activities limited a little: Age 16 to 64 %	0.18		0.95		0.11	
Day-to-day activities not limited: Age 16 to 64 %	0.04	-0.03	0.63		0.05	
Provides no unpaid care %	0.49		0.36		0.44	
Provides 1 to 19 hours unpaid care a week %	0.86		0.28		0.92	
Provides 20 to 49 hours unpaid care a week %	0.27		0.46		0.13	
Provides 50 or more hours unpaid care a week %	0.06		0.41		0.09	
Main language is not English	0.00	0.05	0.02	0.11	0.00	0.05
Density (number of persons per hectare)	0.93		0.14		0.43	

Table 35: Association between socioeconomic status and readmission risk at 30 days

	Mortality all diabetes		Mortality T1DM		Mortality T2DM	
	TTEST	Cohen's D	TTEST	Cohen's D	TTEST	Cohen's D
% not deprived	0.17		0.49		0.00	-0.08
% deprived in 1 dimension	0.12		0.24		0.01	0.05
% deprived in 2 dimensions	0.14		0.84		0.00	0.07
% deprived in 3 dimensions	0.03	0.04	0.36		0.00	0.08
% deprived in 4 dimensions	0.02	0.04	0.25		0.00	0.08
% Adults in employment	0.50		0.74		0.02	0.04
% Ethnic minority race (Not English)	0.00	0.05	0.07		0.00	0.09
Day-to-day activities limited a little %	0.29		0.57		0.95	
Day-to-day activities limited a lot %	0.00	-0.08	0.69		0.01	-0.05
Day-to-day activities not limited %	0.01	0.05	0.61		0.25	
Day-to-day activities limited a lot: Age 16 to 64 %	0.04	0.04	0.38		0.00	0.05
Day-to-day activities limited a little: Age 16 to 64 %	0.23		0.80		0.01	0.05
Day-to-day activities not limited: Age 16 to 64 %	0.00	0.06	0.72		0.15	
Provides no unpaid care %	0.01	0.05	0.37		0.03	0.04
Provides 1 to 19 hours unpaid care a week %	0.02	-0.04	0.34		0.01	-0.05
Provides 20 to 49 hours unpaid care a week %	0.78		0.76		0.01	0.05
Provides 50 or more hours unpaid care a week %	0.23		0.76		0.96	
Main language is not English	0.01	0.04	0.05		0.00	0.09
Density (number of persons per hectare)	0.19		0.87		0.12	

Table 36: Association between socioeconomic status and mortality risk at 180 days

Outcome measure: 30 day readmission		

Hba1c value post discharge	p-value	Cohen's D
All patients with diabetes	0.0088	0.28
T1DM	0.0077	0.44
T2DM	0.19	NA

Time to Hba1c value post discharge	p-value	Cohen's D
All patients with diabetes	0.00006	0.39
T1DM	0.72	NA
T2DM	0.00002	0.33

Outcome mesures: 365 day mortality		

Hba1c value post discharge	p-value	Cohen's D
All patients with diabetes	0.0074	0.18
T1DM	0.00023	0.78
T2DM	0.07	NA

Time to Hba1c value post discharge	p-value	Cohen's D
All patients with diabetes	<0.0001	0.36
T1DM	0.59	NA
T2DM	<0.0001	0.21

Table 37: Assosciation between Hba1c value and monitoring time with 30 day readmission and 365 day mortality

8.3 New Learning

Overall, this research directly creates new knowledge regarding the association between risk factors and outcomes for patients being discharged from hospital, with a diagnosis of diabetes. The knowledge is applicable both to generalised cohorts of patients with diabetes and specific cohorts of patients with diabetes. The first systematic review collates knowledge and creates new learning regarding the extent to which the research literature has described known risk factors for readmission. The second review creates new knowledge comparing the differences in the extent of the research literature between readmission risk factors and mortality risk factors. New knowledge is created regarding the strengths of association between different risk factors identifiable from a typical electronic health record for different cohorts of patients being discharged with diabetes and in relation to different outcomes and demonstrates the use of standardised effect sizes in this context. New knowledge is also generated regarding the association between socioeconomic geography and negative outcomes when patients are discharged from hospitals with diabetes. Similarly, new knowledge is created regarding the association of glycaemic control and time to testing with poor outcomes, when patients are discharged from hospital with a diagnosis of diabetes. Finally, this discussion chapter presents a summarised version of the effect size measures, noted for the diverse range of risk factors considered within the work. The author believes this being the first example of such an approach. This learning can help work towards identifying potential targets to improve the readmission process for patients with diabetes as well as designing future research projects, which are discussed later in this chapter.

8.4 Limitations

It is important to consider the limitations of the research approach and learning, identified here. This is, in addition, to specific limitations that have been outlined separately in the individual chapters.

Perhaps the most important limitation of this research is the single-centre nature of the data extraction, used to generate the results. Indeed, the readmission systematic review identified that 41% of papers, identified in that search, were also limited to single centre data sources. This has important implications for the research and the findings, as it may be difficult to generalise the findings across different healthcare organisations or different healthcare settings, nationally or internationally. To some extent, there is some mitigation in the research approach here, given the long period over which data was extracted (3 years) and the large number of readmissions studied. It is also important to note that the Coventry & Warwickshire region represents a diverse population group, which adds some robustness to the research findings. However, it is, of course, essential however to ensure that the research findings described here are reproducible in other healthcare settings or organisations. Indeed, a key suggestion would be that the further work, as described below, is conducted at a regional scale, which could indeed remain in the West Midlands region with a collaboration between the 3 major academic NHS centres (University Hospitals Birmingham NHS Trust, University Hospitals Coventry & Warwickshire NHS Trust & University Hospitals of North Midlands), alongside the smaller district general hospitals. This would encompass approximately 20 NHS sites, across this NHS region. A similar limitation is that the data, extracted for this research, was reliant on hospital or secondary care data. Given the nature of the research considering discharge from hospital, this was a sensible starting point as all patients, by definition, must have been admitted to hospital and therefore a significant amount of their data would be stored on the hospital electronic record system. However, Community or General Practice data may add more information and greater richness to the data used in the research here, and would help ensure that we meet the PPI panel's opinion that the discharge process is a true continuum and not simply an endpoint in the inpatient care process. Whilst widening the number of NHS organisations, contributing data to the research,

would increase the robustness and generalisability of the results produced it is important also to note that this would represent a significant challenge. In particular, challenges would exist around the different ways in which data is stored and transferred (inter-operability challenges) and challenges around variations in the approvals processes needed to access data (information governance challenges). Neither set of challenges are insurmountable but to include data from a large number of secondary care organisations and access primary care datasets outside of registry sets, such as the THIN dataset [286], would present future researchers with significant challenges, particularly if there was an ambition to continue with anonymised datasets for the purposes of ethical approval.

In addition to limitations around the number of sites, from which data have been sourced, there are also limitations in terms of the dependent variables selected for study. The combined systematic reviews identified 82 unique risk factors for readmission, when patients are discharge from hospital with diabetes. This thesis did not set out at any point to consider all possible risk factors, but only a selection of pre-specified risk factors, as outlined within the Research Approach Chapter (Chapter 2) of this thesis. This was based on both the need to keep a containable piece of work, within which to generate meaningful and properly researched new learning, but also based on limitations of data availability. Different electronic patient records vary in terms of the data availability recorded within them. For example, the UHCW electronic patient record system, used for this research, includes a comprehensive collection of data around biochemistry (and thus Hba1c values), collected both at the hospital and in the local community. In contrast, the electronic record includes very little information around the medications a patient took whilst they were an inpatient, which the systematic reviews, in chapter 3 and 4 identified as being an area of interest in relation to mortality and readmission. This will be a future area of research as newer EHR systems include comprehensive electronic prescribing functionalities, allowing ready extraction and analysis of this medication related data [287].

The final limitation, which is important to discuss, is the issue around association and causation in relation to the outcomes of interest. This PhD thesis is specifically focused on using routinely collected electronic patient record, in order to consider associations between potential risk factors and outcomes for patients being discharged from hospital. The research does not look to establish a causal link between the risk factors

and the outcome of interest. To achieve this would require a significantly different research approach to that described here that both controls for confounders and potentially considers a prospective study design to ensure all relevant confounder data can be collected in structured and systematic fashion. The research must be interpreted in this context, nevertheless, the identification of association is important on the basis that this can form the foundation for future development of risk prediction tools and algorithms described in more detail below.

8.5 Future Work

The data, used within this PhD, focuses specifically on numerical data. This follows the datasets most commonly used within the systematic reviews described at the start of the thesis. This is likely based on the relatively ease of extraction and analysis of quantitative data from electronic health record systems. It is important to note that, in addition to quantitative data there is a wealth of other data sources within electronic record systems, which could be applied to the context of discharge and diabetes. These datasets may include narrative text, (which would be important in the analysis of discharge letters produced by clinical teams at discharge), images both from photographs and radiological imaging datasets, as well as metadata relating to the discharge of patients. There is undoubtedly the potential for individual (or multiple) research projects, within each of these data types, in relation to discharge from hospital for patients with diabetes. Whilst the analysis of such datasets may be more complicated than quantitative data, they are readily extractable from a range of electronic health record systems.

The final experimental chapter (chapter 7), in the thesis, noted the potential of emerging datasets within diabetes care. These offer another source of potentially important data, in order to understanding associations between risk factors when patients are discharged from hospital with diabetes. The most important of these emerging datasets is likely to be CGM based, where the blood glucose is not measured directly, but is calculated from the glucose concentration of the interstitial fluid around cells. CGM systems are increasing in popularity and increasingly being recommended by policy makers, prescribed by clinicians and used by patients. However, there exists limited research that has considered the use of CGM systems in the inpatient environment, due to the increased costs of these systems and lack of

integration with existing electronic patient record systems or patient monitoring systems [288]. There are, however, a small number of studies starting to utilise data from CGM devices in understanding risks associated with hypoglycaemia, for inpatients with diabetes [289, 290]. The author would argue that there is the important potential to extend such research, in order to consider the discharge process for patients with diabetes. Indeed, as discussed in chapter 7, there is an interesting association between “looser” diabetic controls, being protective both in the inpatient setting and seen here is the discharge setting. Looser diabetic control effectively means allowing a higher average blood sugar level to reduce the risk of harmful hypoglycaemia. Data from CGM devices may help further explain why a higher Hba1c is protective and indeed help quantify the extent to which this is being driven by reduced levels of hypoglycaemia.

The most important direction for future work is the creation of risk prediction tools and algorithms to support the discharge of patients with diabetes. These risk prediction models could be embedded within electronic health record systems, and extract data in real time to inform, both patients and clinicians, of the risks involved with an individual patient’s discharge from hospital. By understanding which patients are at the greatest risk, clinical teams will be able to make better informed decisions and target interventions to those patients who need them the most. This is particularly important in the context of limited resources, currently experienced within the NHS context.

Risk prediction models have been developed in the context of diabetes care; typically those that utilise electronic health record data are created using machine learning methodologies [291]. Risk prediction models have been created in the context of diabetes for predicting development of diabetes [291], predicting renal disease in diabetes [292] and predicting negative cardiovascular outcomes [293].

Early models for predicting readmission, when patients are discharged from hospital with diabetes, have been developed [294]. However, the predictive value of these models is only moderate; for example, a model by Rubin et al has a c-statistic of 0.69, where a value of 0.5 is considered not better a predictor than random chance [124]. One of the key challenges, with diabetes risk prediction tools, is that they fail to rigorously pre-specify the candidate predictor variables. Therefore, this research

thesis represents an essential first step in identifying candidate variables, both from the published research literature and from the extraction and analysis of the data described above. It is hoped that this research will form the foundation for future research, which develops and validates the first United Kingdom based risk prediction model for negative outcomes, when patients are discharged from hospital with a diagnosis of diabetes. The development of such a tool would be essential in managing the excess readmission rates, costs and negative experiences that this population of patients experience each time they leave hospital and were described in such detail during the initial patient public involvement work described in chapter 2.

8.6 Personal Concluding Remarks

The author believes this work has important implications both currently and for the future across healthcare services, health informatics and clinical care. These considerations are discussed below, and speculative in nature, yet are grounded on the findings of the research described above and informed by the various Fellowship activities described in Appendices 2-3. Despite the speculative nature of the suggestions, the author would strongly argue that they merit further investigation and consideration.

A) Healthcare service

This research demonstrates that routine electronic health record data for hospital electronic record systems can be used to support the identification of patients with diabetes discharged from hospital who are at higher risk of readmission or at higher risk of mortality. The author would argue that stewardship of such data carries with it the moral responsibility to ensure discharge processes and follow up plans are made using such data and knowledge. A first step would be to present this information a meaningful way to both patients and clinicians. This would can enable both clinicians and patients to understand risks at an individual patient level and look to develop mitigation measures.

In addition to presenting information about risk, healthcare organisations should look to provide options to reduce risks in those populations suggested to be at the highest risk. Importantly this thesis suggests that deprived populations might be amongst the highest risk in certain circumstances.

A challenge for healthcare services is that this information will typically cross-organisational boundaries, with risks identified in the secondary care setting potentially needing mitigation at the primary care level in the community. The need to cross organisational boundaries can potentially create governance challenges, albeit these are not unsurmountable [295]. The auth would suggest that in order to ensure adequate data transfer to support meaningful risk prediction in primary care, that in addition to the traditional “discharge letter” sent from hospital settings, this should include an inter-operable data set focused around risk prediction for that individual patient.

Finally, healthcare services must also look internationally at exemplars of how best to support high risk populations following discharge from hospital, including in particular wider use of tele-health and telemedicine approaches as observed in my fellowship in the Basque Country (Appendix 3) although more typically elsewhere restricted to surgical follow up and often still at an early stage of development [296, 297].

B) Health informatics

This thesis has important implications for health informatics. It reinforces existing studies demonstrating the wealth of untapped information stored on electronic health records and suitable for research similar to that described here [90, 91]. Ensuring that such data is available and inter-operable is a key step in utilising such data sources to promote our understanding. It is also the as future electronic health records are either developed, or procured, that the accessibility of such data for approved research studies is maintained, and can be readily accessed by healthcare organisation without needing to go through EHR provider or purchase additional analytics software.

C) Clinical impact and exploitation of the results of this study

This work provides initial useful information that can potentially be incorporated into clinical practice, whilst prospective or multicentre studies in the manner described above are initiated. The author would argue that the most important consideration is that both readmission and increased mortality are potentially predictable at discharge from hospital for patients with diabetes. When discharge is planned for such patients, it is essential that clinicians consider which patients might be at the highest level of risk and what mitigation might be helpful to support that discharge process. This potentially requires a shift in practices from focusing on whether a patient is “fit for

discharge” towards whether a patient is “fit for discharge AND what might maintain that fitness following discharge from hospital”. This thesis suggests patients who might be at greater risk include those from deprived socioeconomic backgrounds, of older age, using illicit substances or with deranged laboratory results. In particularly where are relatively early check of Hba1c is planned for patients to optimise glycaemic control, it should be considered that these patients are also at increased risk of readmission or mortality as well as the complexities of glycaemic control. Those patients therefore from deprived background who we would normally follow up for assessment of glycaemic control should be the key group to whom we target additional interventions and support.

8.7 Conclusion

Diabetes is increasing in prevalence, internationally, and is associated with rapidly increasing care costs. Patients with a diagnosis of diabetes in hospital are at an increased risk of negative outcomes both during their hospital stay and following discharge. The excess rate of readmission for patients with diabetes places a significant burden on healthcare services, not to mention the human impact on patients and their carers. This PhD thesis uses routinely collected electronic health record to identify and describe associations between risk factors for negative outcomes when patients are discharged from hospital with diabetes. The better understanding of such associations will form the foundation for future research, which allows us to improve patient experience, improve patient outcomes and reduce costs. The research is focused on diabetes, being a truly data rich pathology with a wealth of readily extractable clinical information; however, the approaches developed here can be readily replicated for other chronic conditions to help improve healthcare systems holistically. It is the author's ambition that the next step in the research process is the development of rigorous risk prediction tools that in real-time can predict the risk of negative outcomes and thus use patient data to enable better-informed, personalised healthcare at the point of discharge from hospital.

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Appendix 1: Raw Data Availability Statement

Data was generated from the inpatient electronic health record patient-data of University Hospitals Coventry & Warwickshire NHS Foundation Trust. As is typical for data sets of this nature, whilst the information is anonymised, the ethical approval process requires analysis and storage of the raw data on secure NHS equipment due to the risk of inadvertent or indirect breeches to anonymization. The data is not therefore included as an appendix or supplementary material to this thesis. The raw data may potentially be available from University Hospitals Coventry & Warwickshire NHS Trust subject to approval, ethical review and secure storage arrangements.

Appendix 2: Winston Churchill Memorial Trust Fellowship Report

NHS in Transition: Patient Centred Digital Health and Personalised Care

Dr Timothy David Robbins

Fellowship Report

WINSTON CHURCHILL MEMORIAL TRUST

Contents

Abbreviations

BA – Bachelor of Arts

BM BCh – Bachelor of Medicine and Surgery

CCIO – Chief Clinical Information Officer

EHR – Electronic Health Record System

GMC – General Medical Council

HITECH - Health Information Technology for Economic and Clinical Health Act

ICT – Information Communication Technology

MBA – Masters in Business Administration

NAO – National Audit Office

NHS – National Health Service

NpfIT - The National Project for Information Technology

PCORI - Patient-Centered Outcomes Research Institute

RCP – Royal College of Physicians

RCT – Randomised Controlled Trail

SMS – Short Messaging Service

UK – United Kingdom

USA – United States of America

WCMT – Winston Churchill Memorial Trust

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Finally I would like to thank my family, both my parents **Peter & Eileen Robbins** and Fiancé **Rosie Tucker** for such love and support throughout this Fellowship year.

Biography

My name is Tim Robbins, I am 29 years old, currently living in Royal Leamington Spa in the West Midlands. I work as an Academic Specialist Registrar in Diabetes and Endocrinology at University Hospitals Coventry and Warwickshire NHS Trust. I completed my pre-clinical and clinical training at the University of Oxford, graduating from Brasenose College initially in 2009 with a First Class BA in Medical Science, and then with BM BCh in 2012. I completed an Academic Foundation Programme Training and an Academic Clinical Fellowship with Warwick University Medical School, incorporating a Master's Degree in Health Sciences, form which I graduated in 2017. I am currently jointly working at a Clinical Doctor and pursuing a PhD with The Institute of Digital Healthcare, part of Warwick Manufacturing Group.

I am passionate about the successful adoption of digital technology into healthcare, particularly how to most effectively use the enormous amount of data we currently collect from our patients. I have been fortunate to publish research articles, present nationally and internationally in this area, with my current research focusing on how to most effectively utilise data to improve the discharge process for patients with diabetes.

I am engaged to Dr Rosie Tucker, who is also a practicing doctor. Together we enjoy exploring the outdoors, cookery, golf and looking after our two kittens – Luna & Fleur.

Contact: [redacted]

Executive Summary

Healthcare within the United Kingdom continues to experience enormous pressure, driven from the increasing clinical demands of an ageing population. Healthcare as an industry has been slow to adopt the benefits of innovative digital technologies, often due to the complexities of existing non-digital systems and confidentiality concerns. Digital technologies however offer potentially profound benefits to healthcare systems benefitting patients, clinicians and healthcare organisations. The United States has invested significant resources into the development of digital healthcare environments and there is enormous scope for the United Kingdom to learn from what has worked and what has not worked so well.

This Fellowship incorporated visits to The American Diabetes Association, Banner Health, Cerner Corporation, Harvard Medical School, Beth Israel Deaconess Medical Centre, The Patient Centred Outcome & Research Institute, Boston Start-up Week, MassChallenge and Brigham Women's Hospital Innovation Team. Through semi-structured qualitative interviews with both the leaders and front line clinicians of these organisations six reflective themes considering the successful adoption of digital healthcare interventions were identified:
A. Patient engagement in the development of digital healthcare environments B. Clinician engagement in development of digital health environments C. Entrepreneurship & innovation D. Data in digital health environments E. Informatics training pathways for clinicians F. Dangers of wholesale adoption of USA practices into the UK
These themes, discussed in detail within this report supported the development of 10 key summary recommendations for dissemination and implementation within the United Kingdom, whilst offering considerable scope for further research. The key recommendations are outlined below and explained in more detail throughout the report:
1. We must engage patients meaningfully in the development and delivery of digital health innovations and environments. Once created these digital innovations have the enormous potential to engage patients directly in their care, increasing quality of care and reducing costs of care. In achieving this we must be truly diverse in our engagement activity, being particularity careful to engage hard to reach groups.

2. There is incredible opportunity to build emotional design into our digital innovations and environments, this requires considerable transparency, however the trust that is placed in UK clinicians provides an excellent foundation.

3. As the healthcare environment becomes increasingly digital there will need to be changes to how generalist and specialist clinicians are trained. Frequent rotational changes will prove a barrier to effectively and efficiently using electronic health record systems and further frustrate trainees.

4. Clinical informatics training pathways and clinical informatics career models are urgently needed, potentially developing recognition as distinct speciality within the UK Healthcare Environment. The Faculty of Clinical Informatics is potentially an ideal place to lead such work with the engagement of both trainees and patients.

Page 8

5. There is a need for all clinicians to have an awareness of cyber-security measures and contingency plans. Future informatics trainees need to have a deeper understanding built into

their training curricula, who may be well placed to lead in disseminating key messages to other trainees and clinicians.

6. Clinical informatics trainees and CCIO's need to ensure that non-clinical ICT Leaders are better known to their frontline clinical staff to support engagement and communication.

7. The concept of Quality Improvement Projects, completed by each individual trainee and assessed against fixed methodological criteria needs to be re-evaluated for a digital age, with a preference for collaborative working across care environments and industrial sectors.

8. Work is needed to re-evaluate the research evidence hierarchy pyramid, increasing the value of retrospective research that can capitalise on exceedingly large diverse data sources.

9. Explorative work is needed to consider the value of meta-data contained within NHS data sources to identify opportunities for improved care processes.

10. We should capitalise on the opportunity to develop a bespoke UK digital healthcare environment that is developed from learning internationally but focused specifically on the needs of our patients and future workforce. The systems within that environment must excel at transferring data across boundaries including from non-healthcare sources.

Introduction

Why is it important?

The National Health Service (NHS) in the United Kingdom faces unprecedented challenges. There is an increased demand for clinical care, and yet a shortage of beds to provide that care in. It is estimated there are a third fewer beds and yet that there were 25 years ago (Imison, 2012) despite a 37% increase in emergency hospital admissions (Royal College of Physicians, 2012). It is thought that a significant driver for this increased clinical demand is that our patient populations are getting older, with increased co-morbidities, indeed 65% of people admitted to hospital are now over 65 (Cornwell, 2012). This challenge is being reflected in the workforce with 27% of Medical Registrars (the same grade as myself) reporting that their workload is unmanageable (Royal College of Physicians, 2012). The General Medical Council has since issued guidance that healthcare in the UK has reached a "Crunch Point" in the challenge of matching increased demand with the supply of services and workforce. (GMC, 2017).

Despite these challenges there are enormous opportunities within the NHS. More money is being spent on the NHS in real terms than ever in its history. We now spend an average of £2,160 per person, per year on health care. Whilst this is less than many other similar economically developed countries, it is essential to ensure this spend per capita is used in the most effective manner possible (NIESR, 2017).

A key opportunity for healthcare is looking towards the benefits of digital health. Healthcare is one of the slowest industrial sectors to have adopted digital technology. In 2015 for example 71% of all UK citizens had a smartphone and 88% of adults used the internet (Ipsos MORI, 2015), yet just 2% of the population reported any digital transaction with the NHS (Nuffield Trust, 2016). There is however significant demands among the general population for access to digital health services – with 90% stating they would use a digital service enabling them to ask a clinician a question, 80% would like to view their medical records online & 60% would monitor their disease using a mobile app were that possible (Patient.co.uk, 2012).

In addition to the general population's positive perceptions towards the adoption of digital healthcare, there are profound benefits to the healthcare system as a whole, with the potential to help mitigate increasing demand and reductions in certain areas of supply. In particular digital health interventions can improve both the efficiency and quality of clinical care. The Nuffield Trust is collaboration with KPMG have clearly delineated the potential of digital health benefit the NHS by: (Nuffield Health, 2016):

1. Enabling more systematic, high quality care
2. Delivering More proactive targeted care
3. Facilitating Better co-ordinated care
4. Encouraging Greater patient engagement
5. Improving resource management
6. Delivering system learning and improvement

If digital health interventions can support the delivery of these domains, the NHS may be able to continue to drive forward meeting the increasing demands of patient care, whilst maintaining the quality and safety of care that was envisaged back in 1948.

The adoption of digital healthcare however is profoundly complex. The National Project for Information Technology (NpfIT) was a £10billion project aimed to achieve broad spectrum digital adoption, however whilst creating benefits in some areas, ultimately it failed to digitise the hospitals and community sectors (House of Commons Committee of Public Accounts, 2013). The NpfIT was branded by some as "The biggest IT Failure Ever Seen" and for many years resulted in some reluctance at investing further in NHS ICT systems (Syal, 2013). A key challenge is that the creation of a digital healthcare system is not the simple introduction of technology and computers, but rather integrating technology with a "re-imagination of workflows." (Nuffield Trust, 2016). Understanding how to do this effectively, and what pitfalls to avoid, will be critical to the successful adoption of digital healthcare to the United Kingdom.

The United States has been able to advance its digital health agenda more fully than the United Kingdom. 46 percent of consumers are now considered "active digital health adopters", who remarkably have used not just one, but three or more digital health tools in categories such as telemedicine and wearables over the course of 12 months (Tecco, 2016). Furthermore, in the hospital sector, the government has vigorously promoted the adoption of digital healthcare technologies (Harrow, 2009). The most prominent US Government commitment to ICT technology in healthcare was the Health Information Technology for Economic and Clinical Health Act (HITECH), which committed $25.9 billion to promote and expand the adoption of health information technology (Blumenthal, 2010). Understanding how this, and other digital health technology has changed the American Healthcare Environment is critical to this Fellowship – both understanding what has worked well, and not so well.

Aims

The aim of this Fellowship was to spend time in diverse leading digital health organisations in the United States, learning about how they have successfully adopted digital health interventions, but also the challenges they faced. The Fellowship Activity targets how the understanding developed could be applied back in the United Kingdom and disseminated as widely as possible.

Objectives

1) Develop a detailed, hands-on understanding of the current USA digital healthcare environment, learning from patients, corporations clinicians and policy makers.
2) Learn about both the opportunities and challenges encountered in developing US patient centred digital health systems. What would they do differently if they started again?
3) Cultivate a transnational sustainable network of individuals who share these passions. Develop this network to share ideas, perspectives and collaborations. In sharing experiences there is enormous potential to benefit patients in the UK, US and worldwide.
4) Widely share learning in the UK at local, regional and national levels; engaging across patient groups, healthcare providers, academic institutions and healthcare industries.
5) Apply this to my own innovations and career. Achieve meaningful, measurable, personalised health process changes nationally. Do this at a critical time for the NHS as it faces enormous challenges and looks towards digital health interventions.

Approach

The approach was to try to gain a holistic viewpoint of the adoption of digital healthcare within the USA, focusing particularly on diabetes as an exemplar disease, but remaining open to learning widely from all sources. The Fellowship was designed with the express purpose to understand digital healthcare adoption from the patient perspective, clinician perspective, academic researcher's perspective, policy-makers perspective and corporate perspective. Whilst such a holistic viewpoint represents something of a challenge to achieve in the short Fellowship Period, it should be noted that there were significant areas of overlap.

The Fellowship was designed as an explorative and reflective period rather than a formal research project however utilising skills developed during my Master's Degree I aimed to take a qualitative approach through structured interviews, focus groups and reflective practice. To encompass the above perspectives, visits were arranged in advance to The American Diabetes Association, Banner Health, Cerner Corporation, Harvard Medical School, Beth Israel Deaconess Medical Centre, and The Patient Centred Outcome & Research Institute. In addition during the Fellowship, I took advantage of opportunities that arose and visits were organised to the Boston Start-up Week, MassChallenge and Brigham Women's Hospital Innovation Team.

The results of semi-structured interviews, observations and meetings from these events was recorded contemporaneously through a journal written record and then thematically appraised to create the results, recommendations and dissemination plan described below.

Thematic Observations & Reflections

The observations and reflections gained during the Fellowship can be grouped into 6 key thematic areas which are listed below, these will be explored individually and their linkages assessed.

1) Patient engagement in development of digital healthcare environments
2) Clinician engagement in development of digital health environments
3) Entrepreneurship & Innovation
4) Data in digital health environments
5) Training for Clinicians in Informatics
6) Dangers of wholesale adoption of USA practices into the UK

1) <u>Patient engagement in development of digital healthcare environments</u>

The Fellowship demonstrated that patient engagement in the development and delivery of digital healthcare environments is critical to success. In the United Kingdom the concept of patient engagement is certainly not new, and has been championed by the National Institute for Healthcare Research (NIHR, 2017). Existing UK patient engagement has however focused primarily on engagement with research processes, rather than engagement within the provision and innovation of routine healthcare services. In the USA, it is quite different, patient involvement is not such a requisite in research however they have explored and actively exploit the benefit of patient engagement in designing and developing services – for instance one hospital had a “The 200 Patients” user group where clinical ideas and services could be suggested, explored and developed.

The PCORI centre demonstrated how patient engagement can be achieved at varying levels within the delivery of a digital healthcare environment – from engagement with an individual patient’s care, to the structure of an organisation, to healthcare policy at regional or national levels and finally engagement during healthcare research.

Digital health development benefits from patient engagement, but also can facilitate it, and there were case studies demonstrating the potential success of engagement at different levels. For example, failure to attend clinic appointments in the United States represents a major issue there, as it does in the UK, however using digital technologies to engage patients with the booking process such that they can select a preferred time and date can reduce significantly the number of patients who fail to attend.

Central to encouraging greater patient engagement is how to effectively communicate with the patients you are looking to engage. An interesting case-study was that of developing text-message adherence alerts to patients with diabetes, however pilot work demonstrated difficulty in deciding what wording to use for these alerts, successful co-production with patients enabled a tailored wording to be created that would support, without patronising patients, and producing far superior results to the initial project pilot.

In looking to engage patients, for instance in booking their desired clinic times through and on-line portal, or co-producing SMS based reminders there was something of a tendency to

look towards treating patients as consumers, rather than 'unwell patients' seeking healthcare. The increasing drive for "mobile first" solutions to patient engagement was a good example. To some extent this supports engagement as creating a consumer like environment, such as might be found when internet shopping, enables patients to feel more comfortable. A number of electronic health record providers had historically pushed towards this "normal consumer experience" citing it as an aid to engagement. My time at Cerner however was eye-opening in that it illustrated that the assumed benefits of a normal consumer environment may not actually be so readily apparent. Typically when designing a digital service for consumers (e.g. an online shopping platform, or video on demand service) there is a desire from the designer to encourage consumers to both visit initially and subsequently frequently return to the digital service. Similarly when consumers visit these environments they ***want*** to be there often as part of their leisure time. In contrast healthcare is quite significantly different, patients would much rather not be ill, nor having to seek the advice of a healthcare profession, and the healthcare industry aims to reduce re-admissions and re-visits as much as possible. In engaging patients therefore there needs to be quite distinct process and culture compared to the 'normal consumer experience' approach.

The approach being developed by Cerner was therefore really quite refreshing and it focused around two key concepts. The first was designing digital environments to effectively engage patients through breaking healthcare down into "Condition, Venue & Experience" where the aim is to focus on the final patient experience, matched to what meet the patient's needs through their condition and their location of care. Overlaying this was the concept of emotional design, moving beyond simply digital solutions for clinical care but building emotion and empathy into healthcare processes. Successful emotional design they felt often relied on mere moments of care, however too successfully deliver those moments requires intensive pattern recognition based around patients individual conditions, venues and previous experiences.

The delivery of emotional design within a digital healthcare environment engages patients strongly in their care, however requires interaction beyond simply collection of clinical facts such as biochemistry or radiology results. It requires patients and clinicians to engage with emotionally and transparently. To achieve this requires trust. The corporate environment of healthcare within the USA has eroded trust in healthcare professionals and therefore it is interesting to reflect that in the UK, where doctors represent one of the most trusted professors (IPSOS, 2017) it may be easier to capitalise on the profound benefits of emotional digital design.

Whilst patient engagement and emotional design are truly exciting concepts, they are not without challenges. Patients are truly diverse, and successfully engaging with those patients requires engaging with diverse groups. The PCORI Centre highlighted that to date much of the patient engagement around developing digital software has been with white middle class Americans, rather than harder to reach populations. The American Diabetes Association have strong links to these harder to reach populations, who are often most in need of healthcare support. Some are unable to afford Insulin for themselves or their children, unable to afford testing strips to monitor their disease or unable to afford the healthy foods that would support their diabetes care. Similarly a particularly hard to reach population were the prison population who frequently come to The American Diabetes Association for support. These population groups often need written material from the American Diabetes Association and struggle to access digital support interventions, similarly they may struggle to have sufficient time to engage in the development of new digital environments, given much more pressing needs on their time. Time itself can be a challenge to patient engagement in the delivery of digital healthcare interventions. Digital technology is fast moving and the time for development (for

instance of a new app) can be very short before it is out-dated. The organisations I met therefore were trying to see how to engage patients most efficiently in development activities – something that still remains a major challenge.

Whilst undoubtedly there are challenges to patient engagement, successfully achieving it should not be ignored – it concisely summarised to me "that the most effective way to reduce care costs is to recruit patients as part of the care team." Co-producing digital healthcare environments in the UK to achieve this is an opportunity that must not be missed!

2) Clinician engagement in development of digital health environments

The introduction to this report highlighted the challenges faced by healthcare professionals working in the UK, with staff shortages and burnout being key risks. In the United States the retention and engagement of physicians was seen as a major priority and many were surprised by working practices in the United Kingdom. Just as using the development of digital healthcare environments to engage patients, the development of such systems to engage physicians can bring significant benefits.

Electronic health record systems (EHR), which represents the digital interface clinicians use on a daily basis are becoming increasingly complex. There is enormous opportunity to use these systems to support and engage physicians. Many EHR's enable personalisation of their interfaces to enable clinicians to choose how information is presented to them as they log-in, and these interfaces can vary depending on the venue where the clinician is logging in from (e.g. on a ward, in a clinic or at home). Clinicians can personalise the system much more deeply including bespoke short-cuts and auto-filled forms, all designed to support the efficiency of their clinical work and the quality of care they provide. Such personalisation of digital systems was enormously popular with clinicians in the United Sates, however underpins a significant complexity of the clinical systems they are using. These systems take significant amounts of time to learn to use, both through initial training and 'on-the-job-learning.' High retention rates of physicians in US Hospitals gives the time necessary to develop an understanding of these systems. In the UK however junior clinicians for the first 9 years or more of their medical career rotate up to every 4 months, it would be impossible in this context for individual hospitals to engage such physicians fully in their electronic health records if they are moving on so frequently – this represent a major barrier to the introduction of diverse yet complex EHR's to the UK and should be treated with caution.

The EHR's are typically thought to be the digital portal that supports the care of patients, however in the USA they are also used to care for the clinicians. A good example of this was in a primary care context, where the EHR automatically tracks physicians' actions. It can highlight to physicians themselves and their supervisors when clinicians are working unsustainably long hours or logging on frequently in their leisure time to catch up on work. This can support more effective job planning, and avoid the risks of burnout. Similarly where clinicians are not using the system effectively, for instance not using popular short-cuts or pre-formatted forms the EHR can identify this and support physicians to work more efficiently. I was naturally concerned that this might come across as an instruction or "big-brother" concern amongst physicians, but quite the opposite, those I spoke to were very supportive of the systems they were using.

Whilst the digital environment in the United States seemed generally popular, undoubtedly there remains and has previously been elements of conflict. Discussing with both the providers and users of the EHR systems is became apparent that when introducing new digital systems,

careful communication is absolutely critical. A case study is that the new systems enable "order-sets" to be created, whereby when an initial suspected diagnosis for a patients is entered, the EHR automatically suggest which investigations should be ordered, and with as little as a single click, all suggested investigations can be ordered and scheduled automatically. To many lay readers this would seem like an ideal system, and it significantly reduces the risk of important investigations being omitted or forgotten. To clinicians however it can be considered "standardisation" whereby their professional opinion is being over-ruled and patients are not treated as individuals but rather as simply diseases. In the USA however they have overcome this by careful communication with the physicians involved. Rather than terming this approach "standardisation," it is termed "reducing variance" and it is very clearly highlighted that the time saved through this approach enables more time to be spent with the patients identifying and supporting their emotional needs.

Engaging physicians however went beyond simply careful wording and communication, the EHR systems were designed for each healthcare organisation with panels of clinicians. For example the reduction in variation process above requires that each diagnosed condition is matched to the set of investigations that are required and the urgency of those investigations established. This was achieved at the Banner Hospital Group through "Clinical Consensus Groups" where clinicians of different grades and specialties met to agree on these groupings and review the impact of any changes made. These were again popular with clinician engaging them directly in the digital systems.

The Banner Health Group went yet further still and rather than simply having panels of clinicians inputting into the EHR design, they invested significant time and resource into ensuring the could engage in the most effective manner – for many clinicians this involved providing the time and money for them to attend mini-MBA training courses in collaboration with the local University. Leadership was seen to be essential to the successful delivery of digital interventions within this organisation, and it was noted that often ICT professionals are seen as being based in separate (often off-site) buildings and rarely seen on the clinical floor. Leadership through visibility was a major drive in the USA and it was remarkable how well the organisations non-clinical ICT leadership knew the clinicians delivering care on the frontline. This was clearly and exemplar that needs to continue to develop in the United Kingdom.

3) Entrepreneurship & Innovation

The presence of multiple healthcare providers within individual US cities promotes competition. This is competition for attracting patients, recruiting staff members and listing insurers. Such competition drives innovation across care and increasingly digital innovation is at the forefront of such changes. Furthermore the corporate nature of healthcare within the United States has promoted a strong entrepreneurial ethos with individual healthcare organisations small and agile enough to reach out to entrepreneurs to create digital interventions and deliver digital health based change.

There is a strong innovation ethos within healthcare in the United Kingdom, this is driven through "Quality Improvement" methodologies and is distinctly different from the innovation and entrepreneurial approaches observed in the USA. In the UK every trainee is expected annually to complete a Quality Improvement project, this is expected to follow a set Quality Improvement methodology and is assessed as part of their annual competency reviews. Digital Health Innovation in the USA takes a significantly different approach, the projects developed are in no way "individual projects" but rather cross boundaries across healthcare

providers, digital health corporations, patient groups and public sector organisations. The players within the originating healthcare organisation are diverse and work in truly collaborative relationships. Digital Health innovation necessarily requires this approach, as a diverse range of skillsets are required including clinical, managerial, information technology and data science.

The selection of which processes to innovate was also important, in the United Kingdom innovation and quality improvement is often borne out of clinicians' frustrations with existing systems, however my experiences in the USA suggested that might not be the most effective approach to achieving change. The Pulse@MassChallenge Public Private Partnership is a remarkable organisation supported by the local equivalent of a City Council to encourage innovation. Here Healthcare organisations "reverse pitch" their needs to potential innovators and entrepreneurs who suggest innovations and apply for funding from the original healthcare organisation. The Pulse@MassChallenge then provide support to the selected teams to deliver their change effectively and efficiently. This approach identifies that in the challenging healthcare environment, to be truly successful digital innovations need to do more than just save money or improve care, but simultaneously need to address strategic challenges of importance to healthcare leadership teams. It should be noted that the Academic Health Science Networks in the United Kingdom have the potential to develop similar pathways and approaches as Pulse@MassChallenge and truly make the United Kingdom a leader in Digital Health Innovation.

It was notable in the USA that healthcare organisations were not afraid to "think big" in their approach to digital health innovation. This may be something that has for some time been lost in the NHS due to budget constraints or the fallout from the National Programme for Information Technology described above. A good example of this was the Remote Operations Systems at the Banner Hospital Group where Intensive Care Units across the country are linked by in-room video-conferencing to a Remote Operations "Bunker" in Phoenix, Arizona. Here Critical Care Outreach Nurse Practitioners and Intensive Care Physicians provide remote management advice to these locations supported by staff on-site. This enables rapid deployment of highly specialist nursing and medical expertise into centres that would not otherwise be able to benefit. The real-time management of acutely unwell patients, right through to managing cardiac-arrest situations remotely was remarkable to see and a clear demonstration of what can be achieved with digital health innovation.

The creation of digital health environments within US Healthcare systems itself provided an opportunity for innovation of wider healthcare processes. The implementation of electronic healthcare records can either be modelled against existing workflows or be used to create transformation. Modelling against existing systems reduces activation energy, reduces cost, and can be standardised across healthcare organisations, however potentially loses an enormous opportunity to improve care. Conversely care needs to be taken if a "big-bang" approach to digital health systems is adopted alongside a "big-bang" approach to process change. Such approaches can represent substantially more change than an organisation can handle and have serious repercussions. An alternative approach is that as digital systems are developed, the underlying processes they are applied to are assessed and modifications occur gradually in tandem. A good example of this is in the Banner Health Group where the introduction of digital systems identified delays in getting blood test results back and X-rays performed was delaying care. As a consequence the workflow was modified so that patients' bloods are taken at 4am and X-rays performed at 6am so that all information is available for the morning ward round. The opportunity to be discharged from hospital earlier is a sufficient

driver for patients to accept being woken so early in the morning and the cost savings of early discharges readily accommodate the costs of employing staff out of hours.

Undoubtedly the organisations visited suggest digital health innovation and entrepreneurship is becoming increasingly successful in the United States. In discussions with US practitioners as to how digital innovation can be promoted in the UK, there was an interesting insight that all too frequently the risk of doing nothing is an organisational risk, and yet the risk of doing something is a personal risk. Moving away from innovation as an individual project, but rather a collaborative effort has enormous potential to overcome this seeming paradox.

4) Data in Digital Health Environments

Creating successful digital health environments is dependent on handling increasingly large quantities of complex data. The United Kingdom is in a very fortunate position to be able to utilise the data we already collect on patients, based on the fact that the NHS identifies each patient with a unique identifier (the NHS Number). This is an enormous benefit to healthcare in this country and should not be overlooked – it certainly created a significant amount of envy in the United States where patients may have unlinked records with different healthcare records with different providers across the state, country or even within the same city. Whilst the UK potentially has a head start in the effective use of healthcare data, there is a significant potential to learn collaboratively from approaches trialled in the USA.

Central to the effective use of data in healthcare, is the development of effective electronic health records. Electronic health records act as both the interface to clinical data repositories but also act as the broker between different clinical processes, and business systems. The HITECH Acts described above in the USA were critical to the implementation of USA systems and the Meaningful Use Certification further drives standards. The failure of the National Programme for ICT in the UK means we have not benefited from universal high quality effective EHR's, however significant progress is being made in the procurement and development of such systems.

Within the modern healthcare environment using data effectively requires the ability to manage both transitions of care, but also transitions of data. For instance the transition of data between different clinical systems, between different hospitals, or between primary and secondary care. Increasingly the boundaries of healthcare care are becoming more blurred, with patients wishing to utilise their data on third party devices or apps, or add their own data to the healthcare record. It is important to recognise therefore that as the UK proceeds to procure new Electronic Health Records that they are able to integrate and effectively transition healthcare data. I would argue that we need to be selecting or designing EHR's based on their ability to integrate with external apps and services, rather than their usefulness as comprehensive yet closed platforms. It is quite exciting to note that healthcare data systems in the USA have historically been provided by specialist companies due to the complexities of "HIPPA" confidentiality requirements, increasingly though non specialist digital companies such as Apple or Google were reported to be actively pursuing HIPPA Compliance, potentially dramatically changing the digital healthcare landscape of the future.

Increasing the storage and accessibility of data to patients and clinicians whilst transitioning this data across boundaries introduces significant cyber security concerns. My Fellowship travels coincided with the recent WannaCry Ransomware attack that compromised a number of NHS ICT systems nationally, and prompted far more to be shut down to prevent infection or attack (NAO, 2017). At Harvard Medical School, discussions on cyber security noted that

the typical refresh rate for medical computer equipment is very different to non-medical equipment and that unfortunately many ICT systems that were affected had failed to install security upgrade patches. In the USA due to the wider installation of these patches only 2 hospitals were affected. Nevertheless cyber security remains a major concern for USA healthcare networks, who were much more affected by the Petia Virus attack, not because their own systems were affected but because supplier systems often based in the Ukraine were profoundly impaired.

It was clear that US Healthcare Leadership now sees virus attacks as a part of life, and likely to increase in the future. The risk is substantial and if a ransomware attack was to encrypt patient information it would be impossible to identify if that patient information had been moved. Despite this, the suggestion was that a pervasive ransomware attach was only a matter of time and preparedness was key. Healthcare organisations need to consider not just how they would recover, but how they would recover safety critical systems quickly, and achieve speed that whilst protecting their back-up environments (which should those be compromised would prove catastrophic). The recent cyber-attacks however have increased the focus on cyber security both for healthcare leaders in the USA, but also training for clinicians on the ground and changes to working practices. It is important that the UK builds experience along with our USA counter-parts and I would argue there is significant education work to be done amongst clinicians. There was also an important concern that “Bring-your-device” to work policies, which can reduce the cost of implementing new digital environments, may add substantial cyber-security risks and whilst new EHR’s are being procured this should be taken into account.

Whilst there are substantial fears and concerns regarding the risks of increasing healthcare data availability and accessibility, the potential of such sources to benefit our understanding of health and disease is enormous. In particular risk-prediction modelling using large healthcare data sets is transforming understanding of disease and healthcare processes. Notable approaches that were being taken in the USA included automatic, continuous risk stratification to enable personalised care throughout a healthcare journey, rather than the “single point” risk stratification that is often applied in the UK. Furthermore using large data sets incorporating non-clinical data was vital, there is an underused treasure trove of so called “meta-data.” Meta-data is effectively data that sits around a data-point of initial interest; for instance a blood sugar value is a data point of interest, however meta data includes; who entered the value into the system, what time it was entered, how many times it was reviewed, who reviewed it and what actions did users take after reviewing the value. Incorporating meta-data into the ideas described above of emotional or quasi-emotional data collection has enormous research potential.

When considering the research potential of the health data that is increasing in quantity, quality and accessibility, it worth noting that our attitudes to research may need to change. Historically there has been an evidence based hierarchy of research evidence (Petrisor, 2007) with individual case studies at the bottom, followed by retrospective reviews of data a little higher, but the gold standard being randomised controlled trials (RCT’s). RCT’s are considered at the top of the pyramid for their ability to consider causality. This pyramidal structure however was conceived when there was far less data availability, where retrospective data was collected by hand from paper records, not the automated collection of enormous quantities of clinical data and meta-data across care boundaries and indeed beyond. Whilst retrospective data remains unable to identify causality such a powerful resource should not be overlooked and there is a need to reconsider the concept of a pyramid of importance, but rather the concept of different research approaches being optimised for different research questions, and true value coming when they are combined.

5) Training for Clinicians in Informatics

There are clear benefits to the delivery of innovative digital health environments and effective use of healthcare data. The observations discussed already however highlight that to achieve this is complex, requiring collaborations across industries, with patients, incorporating cyber security and meaningful innovation pathways. To meet these complex demands it is essential that there is a clinical workforce well versed in the language, skills and experience needed to manage such interventions and to facilitate patient co-production & engagement.

The USA have recognised clinical informatics as a dedicated healthcare speciality. Clinical informatics can be defined as the transformation of healthcare by analysing, designing, implementing and evaluating information and communication systems to improve patient care and access to care. Clinicians training in informatics in the USA spend roughly 30% of their time on clinical elements and 70% on informatics elements. At the Beth Israel Medical Centre there were 8 informatics fellows. There is an established career path with a defined syllabus, accrediting exams and then expectations that trainees will progress to Assistant Chief Medical Informatics Officers and subsequently Chief Medical Informatics Officers Roles. The Informatics training fellows are a truly valuable resource to the organisations that employ them, often acting as an in-house consulting team for digital health innovation and strategic delivery.

I was fortunate to spend time discussing Clinical Informatics Training with Professor Charles Safran, who is the Chief of Division at the Beth Israel Hospital & Harvard Medical School, as well as the immediate past president of the American Medical Informatics Association. His feeling was that establishing informatics as clinical speciality substantially changed perceptions regarding the role of informatics in healthcare both for trainees and informaticians themselves. During our discussions however it was clear that the training pathway adopted in the USA, might not be the most appropriate pathway to adopt in the UK given differences in clinical training internationally.

Within the UK there is no distinct training programme, although the role of the Chief Clinical Informatics Officer has been developed in a number of organisations, this is supported by “on-the-job” training such as the Royal College of Physicians Chief Clinical Informatics Officer Summer School (RCP, 2017). There is clearly a need to provide those already in post with training, however I would argue a pressing need to ensure training can be delivered in a structured way throughout existing training time for trainees wishing to take up CCIO or similar posts in the future. The Faculty of Clinical Informatics is an organisation being established within the United Kingdom that looks to be a Professional Membership Body for all clinical informatics professionals across the UK. It aims to publish professional standards, support re-validation, provide accreditation and promote professional leadership. It has just appointed is Founding Fellows, first members of staff and held its first meeting. There is enormous potential of this Faculty to support the delivery of a clear training pathway for clinical informatics trainees from medical school to consultant level. Enabling sustainable, rigorous and recognised informatics training within the UK workforce will be essential to the successful delivery of digital healthcare environments for our future patients and the USA provides an excellent example in this regard to learn from.

6) Dangers of wholesale adoption of USA practices into the UK

Throughout this Fellowship report it is evident that there is enormous potential to learn from innovative practice that certain centres in the USA have adopted. It must be warned however that the wholesale adoption of USA practices with regard to digital health innovation should not be taken without due assessment. A good example is given above, whereby the concept of rigorous informatics training and career pathways is invaluable, differences between existing USA & UK medical training mean that in practice a successful UK pathway would look really quite different.

The importance of rigorously assessing concepts and products developed in the United States before adopting similar in the UK goes beyond simply training. The Electronic Health Records, which are at the centre of many Digital Health interventions in the United States were built as a consequence of the HITECH Act and are certified against Meaningful Use Criteria. The HITECH Act and Meaningful Use Criteria were designed with the needs of the American Health System in mind, this is profoundly different to the UK Health System. Adopting too readily American EHR's would therefore mean wrongly adopting the criteria set out by American Policy Makers. Going beyond simply policy, USA healthcare EHR's are often based around "episodes of care" where a patient is admitted, treated and discharged rather than a care journey from birth to death as would be achievable in the United Kingdom. The reasoning behind this is that in the USA healthcare providers bill insurers based around the costs of each episode of care, and therefore the digital systems is created to reflect that. We would potentially look to create something quite different in the UK.

Whilst this is something of a cautionary note, it is actually potentially one of enormous optimism, giving the opportunity to create something in the UK that is truly bespoke for our healthcare services and future patients' needs. It would be foolish not to look and capitalise on the work done in the USA and internationally, alongside many of the successful products that have been developed in the USA however engaging UK patients, UK clinicians and UK trainees to assessing and adapting those products will be essential to the future delivery of care for our country.

Summary Recommendations

1. Clinicians & academics must **engage patients meaningfully** in the development and delivery of digital health innovations and environments. Once created these digital innovations have the enormous potential to engage patients directly in their care, increasing quality of care and reducing costs of care. In achieving this we must be truly diverse in our engagement activity, being particularity careful to engage hard to reach groups.

2. There is incredible opportunity to build **emotional design** into our digital innovations and environments, this requires considerable transparency, however the trust that is placed in UK clinicians provides an excellent foundation.

3. As the healthcare environment becomes increasingly digital there will need to be **changes to how generalist and specialist clinicians are trained**, this will need to be addressed by bodies such as Health Education England responsible for training. Frequent rotational changes will prove a barrier to effectively and efficiently using electronic health record systems and further frustrate trainees.

4. **Clinical informatics training pathways and clinical informatics career models** are urgently needed, potentially developing recognition as distinct speciality within the UK Healthcare Environment. The Faculty of Clinical Informatics is potentially an ideal place to lead such work with the engagement of both trainees and patients.

5. There is a need for all clinicians to have an awareness of **cyber-security measures and contingency plans**, this can be developed during both undergraduate and postgraduate training. Future informatics trainees need to have a deeper understanding built into their training curricula, who may be well placed to lead in disseminating key messages to other trainees and clinicians.

6. Clinical informatics trainees and CCIO's need to ensure that **non-clinical ICT Leaders are better known** to their frontline clinical staff to support engagement and communication.

7. The concept of **Quality Improvement Projects**, completed by each individual trainee and assessed against fixed methodological criteria needs to be **re-evaluated** for a digital age, with a preference for collaborative working across care environments and industrial sectors.

8. Work is needed to **re-evaluate the research evidence hierarchy pyramid**, increasing the value of retrospective research that can capitalise on exceedingly large diverse data sources.

9. Explorative work is needed to consider the **value of meta-data** contained within NHS data sources to identify opportunities for improved care processes.

10. Clinicians & Academics should capitalise on the opportunity to develop a **bespoke UK digital healthcare environment** that is developed from learning internationally but focused specifically on the needs of our patients and future workforce. The systems within that environment must **excel at transferring data across boundaries including from non-healthcare sources.**

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Appendix 3: Albert Renold Fellowship Report

EFSD Albert Renold Fellowship Report – Dr Tim Robbins

Travel Period: 7th October to 27th October 2019. Amount Awarded: Euros 3,037.00
Recipient: Dr Tim Robbins, Home Institutions – Institute of Digital Healthcare, WMG, University of Warwick, UK & University Hospitals Coventry & Warwickshire NHS Trust, Coventry, UK. Host Institution: Kronikgune, Torre del Bilbao Exhibition Centre, Barakaldo, Bilboa, Spain
Area of speciality: Health Informatics & Diabetes Care Delivery

Introduction

Dr Tim Robbins visited the Kronikgune Institute in the Basque Country, Spain. The aim of his visit was to better understand Basque Country's approach to integrated care and digitally delivered integrated care delivery and to apply this learning in the context of UK & international diabetes care. The Basque Country has received special recognition for it's integrated care delivery and is one of a very small number of European regions receiving a 4-star accreditation of it's approach. The Kronikgune Institute aims to "promote and carry out research into the management and organisation of health and social-care services, in line with the policies of the department responsible for health, which pursue the continuous adaptation and transformation of the health system, keeping people at the centre of the system and including the challenges arising from old age, chronicity and dependency."

The learning from the fellowship period can be most succinctly summarised into three overarching themes; (1) a clearly defined health policy that pushes boundaries (2) repeated population wide risk stratification (3) E-health strategies. This report defines the achieved learning under each of these three categories and then describes how this knowledge and the "techniques" described can be incorporated or integrated into diabetes research and diabetes practice innovation in the NHS Context and internationally.

Health Policy that Pushes Boundaries

Basque country health reforms are credited with development of one of the most successful integrated care strategies in Europe. These reforms are based on "Health the People's Right, Everyone's Responsibility. Health Policy in the Basque Country 2013-2020" (HPBC). England's NHS has also stressed the need for effective integrated care to manage chronic disease and multi-morbidity. The NHS's proposed approach has been outlined in the "Long Term Plan" (LTP), released January 2019. The effectiveness of the LTP and implementation strategy will be essential to the NHS's ability to deliver effective integrated care. There is however significant contrast between HPBC (proven highly effective in practice) and the new LTP. Development of both policies took a similar approach of cross-sector engagement. Both approaches stress significant baseline progress already made in life expectancy, efficiency and outcomes, whilst recognising chronic disease challenges. There are similar focuses on priority diseases including diabetes, cancer, obesity, domestic violence and mental health.

A crucial difference is that HPBC outlines conceptual frameworks on which service transformation is based. The frameworks cover health, social determinants and implementation. The LTP does not reframe the conceptual framework, and whilst reduction of health inequality features heavily, it doesn't have the same prominence. In contrast the LTP focuses more on leveraging digital health interventions.

Building on the Basque conceptual frameworks there is the establishment of health as a personal asset and a macroeconomic factor. There is a far stronger focus on civic "co-responsibility". This extends to the Basque "Health in All Policies" approach demanding support from other social structures, whilst the LTP in contrast looks outwards explaining how it "Supports Wider Social Goals."

A key contrasts is HPBC's structured and itemised listing of quantitative indicator goals comparing status quo with end-of-plan targets, this includes health outcomes, core structural and intermediate determinants. The LTP expresses no such quantitative targets, but does include financial targets.

Both healthcare systems therefore outline ambitious plans for development of sustainable integrated care. The Basque model is centred on conceptual frameworks and an overriding focus on health inequalities alongside quantitative outcome targets. The LTP acknowledges the importance of inequality and focuses more on digital delivery of economically sustainable integrated care. It will be important to evaluate progress against these aims alongside the next iteration of the Basque Health Plan in 2020.

Population Wide Risk Stratification

The Basque country have adopted a process of regular population wide risk stratification with ordering of the population according to their expected healthcare need over the next year. To achieve this, healthcare cost is used as a proxy of healthcare need and uses a commercial model provided by John Hopkins University. The use of a universal country-wide integrated electronic health record enables data to be pulled from primary care secondary care tertiary care and community pharmacy data for the entire population. This creates a pyramid traffic-light based summary of a patients predicted healthcare cost. Importantly, linear regression not black box artificial intelligence is used in order to ensure acceptability to clinicians using the tools. There still however remain some concerns regarding the use of cost as an outcome and therefore this is converted into a "predictive index" based on the formula; (Individual Predictive Cost)/(Average Basque Cost).

At the core of risk stratification is a focus on multi-morbidity, with the top of the risk stratification pyramid dominated by patients with multi-morbidity. Within this multi-morbidity process there is specific inclusion and consideration of patients with diabetes, with 140,000 patients with diabetes identified in the Basque Country. The risk stratification process for diabetes patients focuses on whether or not the patient has had a recent hba1c and what that hba1c is.

The output of the risk stratification process is an alert within the country-wide electronic health record (EHR) and a reason for that scoring directly visible within the EHR. There are 16,000 patients in the highest red category. These patients benefit from dedicated high risk patient pathways that support patients both in the community and on admission to hospital. Importantly, clinicians can add patients to directly to these high risk pathway regardless of the automated risk stratification process therefore blending clinical judgement with quantitative risk stratification.

E-Health Strategies

Central to both the Basque Health Policy and the Risk Stratification approach is a highly developed digital health ecosystem that directly benefits patients with chronic disease and multi-morbid conditions such as diabetes. This is underpinned by a country-wide electronic health record called Osabide, which crosses primary care, secondary care, community care and pharmacy based care. This health record includes remarkable digital health interventions for example a social prescribing module that allows communities to collect and input social prescribing opportunities, which can then be digitally prescribed to patients through the EHR itself. The centrepiece to the digital health strategy of the Basque Country is their E-health centre. This E-health Centre is housed alongside the emergency services and staffed primarily by nurses with a comprehensive collection of high quality digitally stalled protocols. What is remarkable about the e-health centre is that (unlike services such as NHS 111) this service is fully integrated meaning not only does it deal with urgent patient calls 24/7/365 on an adhoc basis, however it also enables scheduled calls and interventions across almost all disease areas within the Basque Country. This means that, for example, when a patient leaves a hospital setting with a diabetes diagnosis the hospital team can communicate this to the e-health central team, who from this central location, will call the patient, identify how they are getting on and suggest potential changes. The reverse integration also exists and is regularly used, whereby the e-health centre are empowered directly to book patients into specialist follow up clinics where they feel there is an urgent need, without having to go through a referral or approval process. The service is highly efficient in reducing unnecessary secondary care follow ups or hospital admissions and itself handles approximately 180,000 patient contacts over a 1 year period.

Summary

Diabetes is a chronic condition that increasingly co-exists with other medical conditions in our era of multi-morbidity medicine. It is therefore essential that we develop and design integrated healthcare systems to support patients with diabetes and other multi-morbidity conditions. The Basque Country represents and ideal living lab where organisations such as Kronikgune have been highly effective in developing and piloting integrated care strategies. My own PhD work in predicting complications when patients with diabetes leave hospital has been directly influenced by these experiences, in particular considering the techniques and approaches needed to effectively implement such risk stratification in the clinical environment. Furthermore, the approaches to digital health interventions and health policy development are directly relevant to the UK and international environment. To share this work further we have submitted a collaborative abstract to the International Conference on Integrated Care 2020, and are working collaboratively on 2 journal articles for submission to peer reviewed journals in the coming months.

Most importantly I would like to thank Dr Esteban De Manuel and his team for so kindly hosting me at Kronikgune and The EFSD for providing the financial support to achieve this Fellowship and associated learning opportunities.

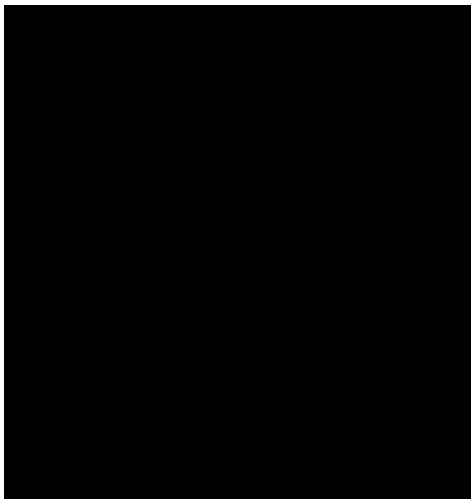
kronikgune
institute for health services research

Torre del BEC (Bilbao Exhibition Centre)
Ronda de Azkue, 1 48902 Barakaldo
Basque Country
www.kronikgune.org

Re: Post EFSD Fellowship Letter – Dr Tim Robbins

Dear Sir / Madam,

This is a post-fellowship letter regarding Dr Tim Robbins' EFSD Fellowship to Kronikgune Institute for Health Service Research from 7th October to 27th October 2019. Dr Robbins spent time at the Kronikgune Institute in Barakaldo as well as external visits to other locations in the Basque Country including Vitoria-Gasteiz, Arrasate-Mondragón & Bilbao. This enabled visits to primary care, secondary care and community e-health care centres in addition to the time spent with the host organisation at Kronikgune. The fellowship was a productive academic experience with the submission of one international conference abstract and the development of two peer reviewed journal articles for submission.



Appendix 4: Ethical Approvals

Research, Development & Innovation Department
University Hospitals Coventry & Warwickshire NHS Trust
4th Floor Rotunda, ADA40017
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

Commercial enquiries: 02476 964995
Governance/Non-commercial enquiries: 02476 966195
Innovation & Communication enquiries: 02476 964748
Research Funding & Grant enquires: 02476 964958
Email: RD&I@uhcw.nhs.uk

28/09/2017

Dr Timothy Robbins
SpR in Endocrinology

University Hospitals Coventry & Warwickshire
Clifford Bridge Road
Walsgrave, Coventry
CV2 2DX

Dear Timothy Robbins

Study Title: Analysing the Risk of Readmission for Patients with Diabetes Discharged from Hospital

Study Ref: GF0220

Thank you for sending in the required documents and completing the GafREC form for the above study. Having reviewed the details of your proposed project, research involving previously collected, non-identifiable information including research undertaken by staff within a care team using previously collected information during the course of care of their own patients or clients, are excluded from NHS Research Ethics Committee (REC) review therefore; I can confirm that we are happy for you to carry out this project within UHCW NHS Trust.

Please be aware that should you wish to change the project in anyway, you must notify our office using the above reference.

I have logged your study on behalf of the Trust, which means you can proceed. I wish you every success with your project.

Yours Sincerely,

[redacted]

Jasmeet Bhambra
Research Administration Specialist

PRIVATE

Dr Tim Robbins
WMG Institute of Digital Health
University of Warwick
Coventry
CV4 7AL

26 November 2017

Dear Dr Tim Robbins

Study Title and BSREC Reference: *Analysing the Risk of Readmission for Patients with Diabetes Discharged From Hospital* REGO-2017-2114

Thank you for submitting the revisions to the above-named study to the University of Warwick's Biomedical and Scientific Research Ethics Sub-Committee for approval.

I am pleased to confirm that approval is granted and that your study may commence.

In undertaking your study, you are required to comply with the University of Warwick's *Research Data Management Policy*, details of which may be found on the Research and Impact Services' webpages, under "Codes of Practice & Policies" » "Research Code of Practice" » "Data & Records" » "Research Data Management Policy", at:
http://www2.warwick.ac.uk/services/ris/research_integrity/code_of_practice_and_policies/research_code_of_practice/datacollection_retention/research_data_mgt_policy

You are also required to comply with the University of Warwick's *Information Classification and Handling Procedure*, details of which may be found on the University's Governance webpages, under "Governance" » "Information Security" » "Information Classification and Handling Procedure", at:
http://www2.warwick.ac.uk/services/gov/informationsecurity/handling.
Investigators should familiarise themselves with the classifications of information defined therein, and the requirements for the storage and transportation of information within the different classifications:

> *Information Classifications:*
> http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/classifications
> *Handling Electronic Information:*
> http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/electronic/
> *Handling Paper or other media*
> http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/paper/.

Please also be aware that BSREC grants **ethical approval** for studies. **The seeking and obtaining of *all* other necessary approvals is the responsibility of the investigator.**

These other approvals may include, but are not limited to:

1. Any necessary agreements, approvals, or permissions required in order to comply with the University of Warwick's Financial Regulations and Procedures.
2. Any necessary approval or permission required in order to comply with the University of Warwick's Quality Management System and Standard Operating Procedures for the governance, acquisition, storage, use, and disposal of human samples for research.
3. All relevant University, Faculty, and Divisional/Departmental approvals, if an employee or student of the University of Warwick.
4. Approval from the applicant's academic supervisor and course/module leader (as appropriate), if a student of the University of Warwick.
5. NHS Trust R&D Management Approval, for research studies undertaken in NHS Trusts.
6. NHS Trust Clinical Audit Approval, for clinical audit studies undertaken in NHS Trusts.
7. Approval from Departmental or Divisional Heads, as required under local procedures, within Health and Social Care organisations hosting the study.
8. Local ethical approval for studies undertaken overseas, or in other HE institutions in the UK.
9. Approval from Heads (or delegates thereof) of UK Medical Schools, for studies involving medical students as participants.
10. Permission from Warwick Medical School to access medical students or medical student data for research or evaluation purposes.
11. NHS Trust Caldicott Guardian Approval, for studies where identifiable data is being transferred outside of the direct clinical care team. Individual NHS Trust procedures vary in their implementation of Caldicott guidance, and local guidance must be sought.
12. Any other approval required by the institution hosting the study, or by the applicant's employer.

There is no requirement to supply documentary evidence of any of the above to BSREC, but applicants should hold such evidence in their Study Master File for University of Warwick auditing and monitoring purposes. You may be required to supply evidence of any necessary approvals to other University functions, e.g. The Finance Office, Research & Impact Services (RIS), or your Department/School.

May I take this opportunity to wish you success with your study, and to remind you that any Substantial Amendments to your study require approval from BSREC before they may be implemented.

Yours sincerely

pp. [redacted]

Dr David Ellard
Chair
Biomedical and Scientific
Research Ethics Sub-Committee

Biomedical and Scientific
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Research & Impact Services
University of Warwick
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http://www2.warwick.ac.uk/services/ris/research_integrity/researchethicscommittees/biomed

pendix 5: Systematic Review Pro-forma (Readmission & Mortality)

Author	Title	Year of publication	Summary	Category (Paper type)	Context	Correctness	Contributions	Clarity	Country of origin	Single centre / regional / national	Number participants	Specific sub-population of people with diabetes	Risk factors found statistically significant	Risk factors not meeting significance but impact	Number of risk factors	Risk factors assessed no impact	Statistical Test	Risk factors identified but no significance test	Notes	Citation